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Book Review.

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FURTHER OBSERVATIONS ON THE ROENTGEN-RAY TREATMENT OF TOXIC GOITER*

J. H. MEANS, M.D., AND G. W. HOLMES, M.D.
BOSTON

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I. INTRODUCTION

A study of toxic goiter with special reference to the results obtained with various forms of treatment, as shown by clinical and metabolism findings, was begun in this clinic in 1914.[1] The forms of treatment that have been studied to date are the surgical procedures of ligation of vessels and partial thyroidectomy, and the exposure of the thyroid gland to the roentgen ray. In this work there has been close cooperation between internist, surgeon and radiologist. Our aim has been to form an unbiased opinion of the relative merits and limitations of the therapeutic measures under investigation.

* From the Medical Service and Roentgenologic Department of the Massachusetts General Hospital, aided in part by a gift from Dr. William Norton Bullard.

1. Means, J. H.: Basal Metabolism and Body Surface, J. Biol. Chem. **21**:263, 1915.

Several reports on this work have already appeared. The earlier metabolism data were published by Aub and Means in 1917,[2] and again in 1919,[3] and by Means.[4] In 1919 Holmes and Merrill discussed the method of giving roentgen-ray treatment, the dangers incident to its use, and the selection of cases.[5] A further report from the roentgenologist's point of view was made by Holmes in 1921.[6]

Our object now is to report in full the clinical and metabolism findings in certain cases treated by the roentgen ray during the last three years, and the end results in cases studied earlier, and to discuss the matter of the roentgen-ray treatment, its value and its limitations as we see them in the light of our experience up to the present time.

Our discussion will be based on forty-four new cases of exophthalmic goiter and fourteen cases of toxic adenoma, as well as on nine cases reported earlier. This group does not include all patients that have been treated by the roentgen ray, but it does include those in which we feel that we have sufficient data to draw an accurate conclusion regarding the action of the roentgen ray. For example, cases with incomplete metabolism data and those in which surgical operations were performed coincident with the roentgen-ray treatment have not been included. The cases treated by surgery alone or by surgery and the roentgen ray at the same time will be discussed by our surgical colleagues in separate papers. The present discussion of the results of roentgen-ray therapy should be read in conjunction with those on surgery when they appear.

II. HISTORICAL

The discovery of the roentgen ray was announced by Röntgen in December, 1895. The significance of this discovery for medicine was grasped almost at once, and although at first attention was centered chiefly on its use for diagnosis, we find within the year suggestions that the rays had a therapeutic application as well. Lortet and Genoud,[7]

2. Means, J. H., and Aub, J. C.: Study of Exophthalmic Goiter from the Point of View of the Basal Metabolism, J. A. M. A. **69**:33 (July 7) 1917.

3. Means, J. H., and Aub, J. C.: Basal Metabolism in Exophthalmic Goiter, Arch. Int. Med. **24**:645 (Nov.) 1919.

4. Means, J. H.: Hyperthyroidism: Toxic Goiter, M. Clinics N. America **3**:1077, 1920.

5. Holmes, G. W., and Merrill, A. S.: Treatment of Thyrotoxicosis by Means of the Roentgen Ray, J. A. M. A. **73**:1693 (Nov. 29) 1919.

6. Holmes, G. W.: Some Observations on the Treatment of Hyperthyroidism with Roentgen-Rays, Am. J. Roentgenol. **8**:730, 1921.

7. Lortet, L., and Genoud.: Tuberculose experimentale atténuée par la radiation Röntgen, Gaz. d'hôp. de Par. **69**:787, 1896.

for example, believed that they could attenuate experimental tuberculosis infections, and Thomson [8] and others noted the burning effect of the rays on human skin. In a paper published by Bleyer [9] only two months after the discovery of the roentgen ray, we find an interesting prophecy that because of their resemblance to light the roentgen rays would prove to have their place in therapeutics. Five months afterward Despeignes [10] reported his attempts to relieve cancer of the stomach by the rays and, in July, 1897, Bergonie and Mongour [11] reported their results in cases of pulmonary tuberculosis. Bergonie,[12] in January, 1897, remarking on Thomson's discovery of the roentgen-ray burn, predicted that further study would prove the therapeutic value of the rays. The first successful therapy was probably that of Freund,[13] who in March, 1897, reported his observations on a case of hairy pigmented naevus which he had completely relieved by the rays. He was led to try the roentgen ray in this case because of the observation that the rays apparently could cause alopecia.

We have been unable to determine beyond doubt who was the first to use the roentgen rays in the treatment of goiter. The paper of Beck,[14] who in 1900 reported some observations on cases of nontoxic goiter, is the earliest we have found. In 1902, F. H. Williams [15] reports that he had some encouraging results in the treatment of exophthalmic goiter by the rays. Pusey [16] also was among the pioneers in the irradiation of toxic goiter. It is interesting to note that the roentgen rays were used in goiter earlier than in leukemia, the first observations in the latter disease having been made by Senn in 1903.[17]

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8. Thomson, E.: The Cause of Burns from Roentgen-Rays, Boston M. & S. J. **135**:610, 1896.

9. Bleyer, J. M.: Crook's X and Other Rays; a Problem Yet to be Solved in Therapeutics, New York M. J. **63**:245, 1896.

10. Despeignes, V.: Nouvelle observation de cancer traité par les rayons de Roentgen, Lyon méd. **82**:428, 1896; **83**:550, 1896.

11. Bergonie, J., and Mongour, C.: Les rayons Röntgen ont-ils une action sur la tuberculose pulmonaire de l'homme, Bull. de l'Acad. d. méd. Par. **38**:66, 1897.

12. Bergonie, J.: Les radiations de Roentgen et leur emploi en medicine, J. de méd. de Bordeaux, **27**:37, 1897.

13. Freund, L.: Ein mit Röntgen-Strahlen behandelter Fall von Naevus pigmentosus piliform, Wien. med. Wchnschr. **47**:428, 1897.

14. Beck, C.: Beitrag zur Diagnostik und Therapie der Struma, Fortschr. a. d. Geb. d. Röntgenstrahlen **4**:122, 1900.

15. Williams, F. H.: Roentgen Rays in Medicine and Surgery, Ed. 2, New York, Macmillan Co., 1902.

16. Pusey, W. A., and Caldwell, E. W.: Practical Application of Röntgen Rays in Medicine and Surgery, Philadelphia, W. B. Saunders Co., 1903.

17. Senn, N.: Case of Spinomedullary Leukemia Successfully Treated by Use of the Roentgen Ray, Med. Rec. **64**:281, 1903.

In 1905, several papers appeared, among others those by Stegmann [18] and by Görl.[19] The latter makes the definite statement that the roentgen ray has a definite action on the thyroid, but adds that further study will be needed to show in what types of goiter it should be used. In the same year Abbé [20] reported a case of exophthalmic goiter in which radium had apparently been of value.

In 1907, C. H. Mayo [21] made the following statement: "We also make use of the roentgen ray. From its known action on the lymphatics and the glands it exerts a favorable effect on the overactivity of the thyroid in exophthalmic goiter, and in some cases seemingly develops something of a capsule and partially changes the character of the tumor. While its effect may not be permanent, it is a valuable adjunct in preparing advanced cases for surgical procedure." In the same year Freund [22] concluded that "roentgentherapy fulfills the causal indication in exophthalmic goiter in that it causes the morbid thyroid to dwindle. It works favorably on the body weight and on the nervous symptoms, and can diminish other symptoms such as palpitation, goiter and exophthalmos. Soft vascular goiters give the best prognosis, the symptoms clearing the more quickly the more recent they are." (Translation ours).

Pfahler,[23] who was among the early workers in this field and also has kept up a consistent interest and study to the present time, was able in 1908 to collect fifty-one cases from the literature, forty-two of which showed good results after roentgen-ray treatment. His conclusions at that time were: "1. Decided improvement may be expected in about 75 per cent. of the cases. 2. This improvement consists of an increase in weight and strength and gradual disappearance of Basedow symptoms. 3. Some improvement should be noted in a month and after from six to twelve treatments. 4. When the treatment is properly given there appears to be no danger, and I can see no objection to recommending the trial of a month in all cases."

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18. Stegmann, R.: Die Behandlung der Struma mit Röntgenstrahlen, München. med. Wchnschr. **52**:1247, 1905.

19. Görl, L.: Ein neues Feld für die Radiotherapie (Strumenbehandlung), München. med. Wchnschr. **52**:944, 1905.

20. Abbé, R.: Exophthalmic Goiter Reduced by Radium, Arch. Roent. Ray **9**:215, 1905.

21. Mayo, C. H.: Goiter with Preliminary Report of 300 Operations on the Thyroid, J. A. M. A. **58**:273 (Feb. 8) 1907.

22. Freund, R.: Die Röntgenbehandlung der Basedowschen Krankheit, München. med. Wchnschr. **54**:830, 1907.

23. Pfahler, G. E.: Summary of the Results Obtained by the Roentgen-Ray Treatment of Exophthalmic Goiter, New York M. J. **88**:781, 1908.

In 1916 Pfahler and Zulick [24] made a complete survey of the literature to that date. They draw conclusions similar to those of Pfahler eight years before. Among other things they say: "We believe that the trial of treatment (roentgen ray) for one series with an interval of waiting of one month is justifiable in all cases, for if operation is decided on nothing is lost and many operations in this way can be avoided." They also point out that the treatment should be directed toward both thyroid and thymus glands, and they warn against the production of myxedema by too long treatment.

Of the more recent papers we should like to call attention to those of Allison, Beard and McKinley,[25] Fischer,[26] Crile [27] and Schlecht.[28] The first two papers give reports of favorable results from the use of the roentgen ray. Crile, on the other hand, concluded that it accomplished nothing more than rest alone and, therefore, he could see no reason for making use of it in the management of hyperthyroidism.

There is always the danger in the evaluation of therapeutic achievements of a bias on the part of the observer in favor of his own pet method of treatment. The truth in regard to the best treatment for exophthalmic goiter probably lies somewhere between the views of enthusiastic surgeon and enthusiastic radiologist. We have made an honest attempt to avoid such a bias in this paper, and later on our thyroid committee (which is described below) will, as a whole, make a report which, from the composition of the committee, is bound to be fairly free from bias. The conclusions of Schlecht seem to us to be of this sort. They are not unlike those that we have drawn on the basis of our own experience, and are as follows:

> A cure of exophthalmic goiter in the sense of a complete restoration of the normal condition is not to be aimed at by roentgenotherapy, but nevertheless we are in a position to expect extensive improvement. Unadapted for such management are only the severest cases, in those especially, in which there already exists a grave cardiac insufficiency. In other respects we stand in the position with all cases of exophthalmic goiter, first of all to try a course of interval therapy in which the roentgen-ray procedure plays a prominent rôle, but without the neglect of the other usual methods of treating the disease. Material improvement of the general condition, subsidence of the subjective nervous symptoms, restoration of the capacity for work, will often be achieved by roentgenotherapy.

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24. Pfahler, G. E., and Zulick, J. D.: The Treatment of Exophthalmic Goiter by Means of the Roentgen Rays, Am. J. Roentgenol. **3**:63, 1916.

25. Allison, R. G.; Beard, A. H., and McKinley, G. A.: Roentgen-Ray Treatment of Toxic Goiter, Am. J. Roentgenol. **8**:634, 1921.

26. Fischer, J. F.: The Roentgen Treatment of Morbus Basedowii, Acta Radiol. **1**:179, 1921.

27. Crile, G. W.: Surgery versus Roentgen Ray in the Treatment of Hyperthyroidism, J. A. M. A. **77**:1324 (Oct. 22) 1921.

28. Schlecht, H.: Die Röntgentiefentherapie in der inneren Medizin, München. med. Wchnschr. **67**:800, 1920.

Among other things, objectively one sometimes sees a decrease in the eye signs, without, however, their entire disappearance. Only in rare cases will the struma materially diminish. (Translation ours).

To the literature of the calorimetry of thyroid disease we can refer but briefly. The elevated metabolism in hyperthyroidism was discovered by Magnus-Levy [29] in 1895, and during the next twenty years a certain amount of research was done, but it was not until after the publication of the surface area formula of the Du Boises [30] in 1916 that the calorimetry of thyroid cases became a common clinical procedure. Since 1916, but more especially during the last three years, an extensive literature on the subject has appeared. The significance of basal metabolism as a functional test of the thyroid has been discussed sufficiently in other papers from this clinic.[31]

III. METHODS

Thyroid Clinic.—All patients with thyroid disease coming to the Massachusetts General Hospital are referred to a special thyroid clinic, where they are seen by members of the medical, surgical and roentgen-ray staff in consultation. A program for the treatment of each case is mapped out, and the period of treatment and study begins. An attempt is made with all new cases of toxic goiter to start with a period in the hospital ward. This is not always possible. Special records are kept of the clinical condition and progress of each patient, and frequent observations of the basal metabolism are made. The members of the staff holding these thyroid clinics constitute a committee for the study of thyroid disease. As pointed out earlier, this report is merely one phase of the work of this group. It is published now because it seems sufficiently advanced to warrant certain definite conclusions. These conclusions have been concurred in by the surgical members. It is proposed, however, to publish later a combined opinion of the committee as a whole on the treatment of toxic goiter in all its aspects.

Calorimetry.—The calorimetry is carried out with apparatus of the Benedict type; the technic used has been sufficiently discussed in

29. Magnus-Levy, A.: Gaswechsel bei Thyroidea, Berl. klin. Wchnschr. **32**:650, 1895.

30. Du Bois, D., and Du Bois, E. F.: Formula to Estimate Approximate Surface Area, Arch. Int. Med. **17**:863 (June) 1916.

31. Means, J. H.: Studies of the Basal Metabolism in Disease and Their Importance in Clinical Medicine, Boston M. & S. J. **174**:864, 1916; Determination of the Basal Metabolism as a Method of Diagnosis and a Guide to Treatment, J. A. M. A. **77**:347 (July 30) 1921. Means, J. H., and Burgess, H. W.: Basal Metabolism in Nontoxic Goiter and in Borderline Thyroid Cases, Arch. Int. Med. **30**:507 (Oct.) 1922.

earlier papers.[32] The normal standards of the Sage Institute are used for comparison with the patients' metabolism.[33]

Method of Treatment.—In treating our cases of toxic goiter with the roentgen ray, we have proceeded on the principle that the effect of the radiation will be greater (1) the larger the amount of radiation absorbed, and (2) the more active and less stable the cells composing the gland are at the time of exposure. In developing our technic we have kept these principles constantly in mind. To obtain the largest possible dose without injury to the skin, we have used rays of relatively short wave length, a long target skin distance and three or more portals of entry. In the selection of cases, only those have been chosen for treatment which showed definite signs of glandular hyper-activity (both clinically and in the metabolism).

The formula for dosage has been varied somewhat in individual cases, and has been changed from time to time in attempts to increase the effect. At no time has the accuracy in measuring the dose been all that could be desired. Some of our failures at least may be due to insufficient dosage, as we have been especially careful not to produce a permanent injury to the skin. With a probable error in dosage of 25 per cent., if we continually avoid an overdose, the resulting dose may be sometimes as small as 50 per cent. below that intended. The skin of patients suffering from hyperthyroidism is more sensitive than the skin of normal persons. We have found a reduction of at least 25 per cent. necessary if reddening and tanning are to be avoided, and it has been our experience that even the slightest tanning may be followed by permanent injury to the skin, such as atrophy and telangiectasia. Any tanning or reddening, therefore, must be avoided in all but severe cases in old women and in men.

The effect of the radiation is undoubtedly increased by repeating exposures, and if the exposures are given oftener than once in three weeks the effect is cumulative.

Taking advantage of this fact, we have tried following the original dose by fractional doses sufficient to keep the tissues saturated, but in the small number of cases tried, we have not observed any improvement over the usual method of exposure. Whatever the method employed is, it is not advisable to continue the treatment beyond five months, unless very definite benefit has been obtained.

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32. Means, J. H.: Studies of the Basal Metabolism in Obesity and Pituitary Disease, J. M. Research **32**:121, 1915. Means, J. H., and Woodwell, M. N.: Remarks on Standards for Normal Basal Metabolism, Arch. Int. Med. **27**:608 (May) 1921.

33. Aub, J. C., and DuBois, E. F.: The Basal Metabolism of Old Men, Arch. Int. Med. **19**:823 (June) 1917.

In the majority of cases reported in this paper, the exposures have been made at 8 inch target skin distance, using a Coolidge tube energized with a rectified current of a voltage capable of breaking an 8 inch air gap between blunt points. The rays have been filtered through 4 mm. of aluminum and one thickness of sole leather. The exposure time and the number of milliamperes passing through the tube are varied somewhat, but their product has been kept fairly constant, from 35 to 40 milliampere minutes being the usual exposure.

For the past year, we have not given any treatment of less than 10 inch target skin distance, and have given several at from 12 to 16 inch distances. This increase of distance, of course, requires a corresponding increase in time of exposure. Three areas are exposed, one on each side of the neck over the thyroid region, and one over the upper part of the sternum in the region of the thymus. The size of the areas exposed has varied considerably but has usually been a square with a diameter of about 3 inches.

Recent studies by Friedrich,[34] Duane [35] and others have shown that increase in the size of the area exposed increases to a considerable extent the effect of the radiation in the deep tissues, because of the amount of secondary radiation produced. Ignorance of this fact, and failure to keep the size of the radiated fields uniform, may have resulted in variation of doses. At present, we are using a measured field.

As already indicated, the interval between treatment has usually been three weeks. Any shortening of this period is likely to produce tanning and should be avoided, except in selected cases.

At each treatment, a prescription indicating the various factors from which the dose is computed is written and signed by the physician in charge of the treatment. The actual giving of the treatment is done by graduate nurses especially trained in roentgen-ray technic. In this way a double check is kept on the dosage. Wooden tables are used to avoid danger from electric shock, and all parts of the patient's body are protected, except the part being treated, from scattered rays by ray proof cloth.

IV. PRESENTATION OF DATA

As we have indicated earlier, this study is based on two groups of cases. One group comprises those cases treated within the last three years; the other group consists of cases treated before the war. The

34. Friedrich, W., and Kroenig, B. (Translated by Schmitz): Radiation Therapy, Ed. 2, New York, Rebman Co., 1922.

35. Duane, W.: Personal communication.

former will serve for an analysis of the early effects of roentgen-ray therapy, the latter for a study of end results.

The data on both groups is given in Tables 1, 2 and 3, the data of the recent group being given in Tables 1 and 2.[36]

To visualize the progress of the disease, charts are rather more easy of interpretation than tables. We cannot take the space to give the individual charts of all our patients. A study of certain composite charts, however, may serve a useful purpose. We will present these first and then discuss certain individual cases to illustrate special points.

THE RECENT SERIES: *Exophthalmic Goiter.*—Of our fifty-eight new cases, forty-four were cases of exophthalmic goiter and fourteen were cases of adenoma with hyperthyroidism (toxic adenoma). It will be best to examine these separately.

Of the forty-four exophthalmic goiter cases, sixteen showed little or no improvement; eight of these came to operation later and were apparently cured. Of the twenty-eight cases in which there was improvement, twelve were apparently cured and sixteen were improved but were not rendered entirely free from hyperthyroidism. No cases seemed to be made worse by the treatment. Two patients who were improved but not cured were later subjected to operation. One of these patients died following operation. So far as we know she is the only patient out of the fifty-eight under discussion who has died.

An impression of the usual effect of the roentgen ray in those cases of exophthalmic goiter in which it has any demonstrable effect (64 per cent. of the cases in the present series) can be obtained from a study of composite charts. In Figure 1 we have shown the composite metabolism, pulse and weight curves of the twenty-eight patients who improved. It will be noted that there is a rapid fall in pulse (from 115 to 89) and basal metabolism (from + 55 to + 21 per cent.) and a corresponding gain in weight (9 per cent.) in the first four months of treatment, during which time the patients received, on the average, five treatments. No further significant drop in pulse or metabolism curves occurred in the next six months, in spite of more treatment. In the second year there was a slight drop.

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36. In this paper, as in the previous papers by Means and Aub,[2, 3, 4] the cases are referred to by their laboratory numbers. In the paper by Holmes,[6] however, they are referred to by the roentgenologic department numbers. So that the reader may identify the cases that appeared in Holmes' paper and in this paper, the following key is given:

Laboratory No.	Roentgenologic No.	Laboratory No.	Roentgenologic No.
224	3646	819	3993
566	3763	621	3611
734	3923	575	3869
628	3933	348	3740

TABLE 1.—Data on Exophthalmic Goiter Cases

Lab. No.; Age; Duration of Disease	Date	Weight, Kg.	Pulse	Basal Metabolism, %	Activity	Roentgen Ray Treatments Dates	Goiter	Exophthalmos	Tremor	Cardiac Condition	Remarks
No. 224	3/29/18	52	125	+85	1	.....	+++	++	++	Compensated mitral disease	Moderately severe. Also chronic cardiac
Mrs. M. J.	4/ 5/18	49	112	+78	1						
Age, 41	4/20/18	48	132	+80	1						
Duration,	1/27/19	62	88	+44	2	Apr. 29, June 10, July 21, Aug. 15, Oct. 18					
4 years	2/ 3/20	64	76	— 2	2	Dec. 17, 1918; Jan. 20, Apr. 21, May 12,					
	12/ 6/20	67	72	+ 2	2	June 3, 1919					
	3/20/22	..	..	....	3	.....	.....	.....	.....	.....	Writes that she is well
No. 316	8/21/19	59	76	+51	1	.....	+	+++	++	Slightly +	Moderately severe. Also cardiorenal
Mrs. E. D.	8/29/19	57	94	+51	1						
Age, 43	12/ 1/19	58.5	76	+28	3	Sept. 8, Sept. 29, Oct. 20, Nov. 10, 1919.....	.....	++	+		
Duration,	3/ 1/20	62	80	+33	3	Dec. 1, Dec. 22, 1919.....	.....	+	0		
2 years	6/28/20	63	88	+25	3	Mar. 1, Apr. 26, 1920.....	.....	.....	.....	.....	Subjectively much improved
	9/15/20	60.5	84	+37	3	June 28, 1920					
	12/20/20	63.5	76	+29	3	Sept. 15, Nov. 13, 1920.....	.....	+	0	.....	Continued improvement subjectively
	12/ 9/21	64.5	74	+24	3	Jan. 12, Feb. 16, 1921.....	.....	.....	.. ...	As before	Chiefly cardiorenal now
No. 319	8/27/19	54	114	+56	3	.....	Rt. +,	Rt. +++,	++	Normal	Recent and mild case
Miss E. C.	12/ 6/19	55	112	+39	3	Oct. 4, Oct. 25, Nov. 15, 1919	Left 0	Left +			
Age, 38	4/24/20	58	92	+20	3	Dec. 27, Feb. 21, Apr. 3, 1920.....	Same	Rt. ++,	+	.....	Looks and feels much better
Duration,	7/ 7/20	58.5	92	+16	3	Apr. 24, 1920		Left +			
2 mos.	10/ 2/20	61.5	80	+ 9	3	.....	0	R.++, L.+	0	.....	Clinically well
	5/14/21	65.5	98	+23	3	.....	.....	Same	... ..	.....	Remains clinically well
	12/17/21	62	102	+26	3	.....	0	Same	+	.....	Started roentgen ray again. Feels well
	2/ 4/22	62	87	+19	3	Jan. 14, 1922.....	0	Same	+	Normal	Improving objectively. Feels well
	2/27/22	62.5	81	+ 5	3	Feb. 4, 22, Feb. 24, 1922.....	.....	Same	... ..	.....	Clinically well
No. 328	9/15/19	52.5	110	+27	2	8 previous treatments.....	++	+	+	Normal	Mild stationary case
Miss T. G.	11/24/19	52.5	116	+39	2	Sept. 22, Oct. 20, 1919					
Age, 25	11/26/19	52.5	100	+39	2	Nov. 24, 1919					
Duration,	11/28/19	52.5	104	+35	2						
2 years	12/ 1/19	52.5	104	+34	2						
	12/ 3/19	52.5	106	+34	2						
	12/12/19	52.5	114	+21	2						
	12/19/19	52.5	112	+26	2						
	3/ 1/20	52	110	+20	2						
	6/20/20	50	104	+31	2	Mar. 1, June 1, 1920					
	11/ 1/20	48	120	+24	1	June 21, July 14, Aug. 4, 1920.....	++	+	+	.....	16 roentgen rayings with no improvement. On October 18, sup. arteries ligated
	12/14/20	45.5	120	+36	2						
	12/23/20	45.5	116	+28	2						
	1/ 6/21	45	114	+35	2						
	3/11/21	45.5	68	— 9	1	.....	.....	.....	.....	..... .	On February 19, subtotal thyroidectomy
	3/22/21	46.5	70	— 4	1						
	11/ 1/21	53	98	+ 7	3	.....	0	+	0	Normal	Clinically well
No. 329	9/15/19	52	120	+73	3	8 previous treatments.....	++	++	+	Normal	Moderately severe. No improvement after 8 roentgen rayings
Mrs. M. R.	3/ 3/20	45.5	128	+66	3	Sept. 29, Oct. 27, Nov. 17, 1919					
Age, 31	3/10/20	45	120	+54	1	.....	.....	.....	.....	.....	No improvement after 11 roentgen rayings
Duration,	3/17/20	44	106	+44	1						
16 mos.	3/23/20	43	112	+54	1						

	4/ 3/20	41.5	116	+45	1		.....	.....	.....	.....	On March 26, sup. arteries ligated
	6/ 7/20	47	108	+45	1						
	7/ 7/20	42.5	96	+15	1		.....	.....	.....	.....	On June 16, subtotal thyroidectomy
	10/ 4/20	50.5	92	+21	3		0	+	0	.....	Clinically much improved
	2/26/21	57.5	98	+21	3						
	5/ 7/21	60.5	92	+24	3						
	11/ 5/21	64.5	80	+14	3		0	+	0	.....	Clinically well
No. 367	10/18/19	56	124	+33	1		++	+	++	Slightly +	Mild, but symptoms increasing
Miss G. G.	10/23/19	56	96	+16	1						
Age, 24	10/24/19	56	98	+18	1	Oct. 23, 1919					
Duration,	10/25/19	56	98	+17	1						
3 years	11/17/19	57.5	120	+38	2						
	12/ 8/19	57	112	+27	3	Nov. 17, 1919					
	12/29/19	58	80	+13	3	Dec. 8, 1919	+	.....	0	.....	Much improved
	3/29/20	55.5	88	+ 7	3	Dec. 29, 1919					
	9/20/20	50.5	80	+ 9	3	Mar. 29, 1920	+	0	0		
	10/25/21	47.5	74	+10	3		.....	.....	.....	.....	Clinically well
No. 374	10/21/19	66	124	+60	2		+++	+	+	.....	Moderately severe. Stationary
Miss A. B.	11/13/19	66.5	120	+70	2	Oct. 21, 1919					
Age, 23	2/ 6/20	62.5	118	+63	2	Nov. 13, Dec. 15, 1919; Jan. 16, 1920	+++	+	+	Not +	Slight improvement after 4 x-rayings
Duration,	4/ 7/20	56	120	+48	1	Feb. 6, 1920	.....	.....		Syst. mur.	On March 6, rt. sup. artery ligated
3 years	6/ 8/20	60	112	+51	2	Apr. 12, May 11, June 1, 1920	.....	.....	.....	.....	On March 20, left sup. artery ligated
	9/27/20	64	116	+40	2	June 24, 1920					
	1/15/21	66	94	+24	3		.....	.....	.....	.....	Objectively better; subjectively not
	3/19/21	66.5	88	+19	3						
	11/16/21	66.5	89	+16	3		0	0	0	.....	Much improved. Married June 4
	4/18/22	72	101	+13	3		0	0	0	.....	Clinically well. Six months pregnant
No. 376	10/22/19	45	122	+45	3		+	+	+	Normal	Moderately severe. Stationary
Mrs. R. N.	1/ 5/20	45.5	114	+54	3	Oct. 22, Nov. 12, Dec. 1, 1919					
Age, 27	3/24/20	46	96	+23	3	Jan 5, Jan. 26, Feb. 16, 1920	.....	.....	.....	.....	Very much improved
Duration,	6/13/20	48	80	+ 3	3	Mar. 24, Apr. 14, May 24, 1920	.....	.....	.....	.....	Clinically well
1 year	11/11/20	49.5	76	+ 7	3		.....	.....	.....	.....	Clinically well
	12/ 8/21	51.5	75	— 2	3		0	Slightest +	0	.....	Clinically well
No. 383	10/29/19	48	98	+21	1		+	++	+	Slight myo-cardial weakness	Mild chronic case. Goiter heart
Mrs. B. S.	1/ 9/20	50.5	84	+21	2	Oct. 29, Nov. 20, Dec. 11, 1919					
Age, 43	6/25/20	57.5	86	+12	2	Feb. 10, Mar. 2, Mar. 23, 1920					
Duration,	11/ 4/20	55	92	+14	2		0	+	0	.....	Improved
3 years	2/17/21	55.5	97	+26	2						
	5/13/21	57	88	+ 5	2	Feb. 18, Mar. 11, Apr. 1, Apr. 22, 1921					
	10/ 4/21	57.5	93	+16	2						
	3/ 7/22	56.5	104	+33	2		.....	.....	.....	.....	Not so well
	4/ 3/22	57	90	+10	2		.....	.....	.....	.....	On March 16, subtotal thyroidectomy
No. 386	10/31/19	51	96	+54	2		++	+	++	Enlarged	Moderately severe. Symptoms increasing
Mrs. R. G.	12/16/19	47	108	+94	2	Oct. 31, Nov. 22, Dec. 15, 1919	.....	.....	.....	syst. mur.	Worse
Age, 33	12/24/19	47	90	+59	1		.....	.....	.....	.....	Improved slightly
Duration,	1/ 5/20	45.5	90	+79	1						
1 year	4/15/20	46.5	98	+69	1	Jan. 5, 1920					
	4/24/20	44.5	86	+53	1		.....	.....	.....	.....	On April 16, sup. arteries ligated
	5/ 8/20	43	80	+42	1						
	6/ 9/20	48	104	+49	2						
	6/28/20	45	100	+59	1		.....	.....	.....	.....	On June 11, subtotal thyroidectomy
	10/20/20	51.5	78	+23	3		.....	.....	.....	Normal	Much improved
	7/13/21	56.5	78	+28	3						
	9/16/21	55	65	+21	3		Sl. on L	Sl. on L.	0	.....	Much improved

TABLE I.—Data on Exophthalmic Goiter Cases—(*Continued*)

Lab. No.; Age; Duration of Disease	Date	Weight, Kg.	Pulse	Basal Metabolism, %	Activity	Roentgen-Ray Treatments Dates	Goiter	Exophthalmos	Tremor	Cardiac Condition	Remarks
No. 389	11/ 1/19	60	120	+76	1	.....	++	+	+++	Not + syst, mur.	Moderately severe
Mrs. A. H.	11/ 8/19	57.5	92	+58	1	Nov. 6, 1919					
Age, 42	11/22/19	56.5	100	+75	1						
Duration,	11/29/19	56.5	96	+60	1	Nov. 24, 1919					
2 years	12/11/19	55.5	96	+61	1						
	12/24/19	54.5	96	+63	1	Dec. 15, 1919.....	++	+	+++	.....	No improvement
	1/ 7/20	54.5	110	+64	1	Jan. 1, 1920					
	1/20/20	52.5	102	+55	1	.....	.....	.....	.....	.....	On January 9, sup. arteries ligated
	2/ 2/20	52.5	100	+39	1						
	2/17/20	52	95	+18	1	.....	.....	.....	.....	.....	On February 9, subtotal thyroidectomy
	2/28/20	52	74	+ 6	1						
	1/22/21	72	84	+ 4	3	.....	0	0	0	.....	Clinically well
	12/20/21	79	92	+15	3	.....	0	0	+	.....	Slight return nervousness. Getting obese
No.408	11/ 7/19	54.5	82	+48	2	.....	0	++	+	Moderate + syst. mur.	Mild stationary case
Mrs. J. J. P.	2/ 9/20	54.5	100	+46	2	Nov. 28, Dec. 19, 1919; Jan. 16, 1920.....	0	+	Less		Subjectively better
Age, 62	10/14/20	55	120	+44	3	Feb. 9, Mar. 1, Mar. 22, Apr. 12, May 4, 1920	0	Less	0	.....	Subjectively much improved
Duration, 3 years	4/10/22	54.5	96	+29	3	Oct. 25, 1920.....	0	Less	0	.....	More improvement
No. 411	11/10/19	63	120	+61	2	.....	+	+	+++	.....	Recent, moderately severe case
Mr. A. S.	12/22/19	63	120	+75	2	Nov. 10, Dec. 2, 1919.....	+	+	+++	.....	Subjectively slightly better
Age, 39	1/14/20	64.5	106	+60	2	Dec. 23, 1919.....	+	+	++	.....	Subjectively further improvement
Duration,	3/19/20	78.5	88	+25	2	Jan. 14, Feb. 4, Feb. 26, 1920.....	.....	.....	.....	.....	Better
3 mos.	10/21/20	74	108	+42	2	Mar. 19, July 12, 1920.....	Less	Less	+	.....	Not so well
	1/15/21	77.5	78	+20	3	Oct. 22, Nov. 13, 1920					
	5/ 1/21	77	87	+46	3	.....	0	0	0	.....	Better, but still slightly thyrotoxic
	4/29/22	79.5	74	+13	3	.....	0	0	0	.....	Clinically well
No. 431	11/29/19	50	106	+29	3	.....	Rt. +	+	++	Not + syst. mur.	Mild and recent
Miss P. R.	1/31/20	50	98	+36	3	Nov. 29, Dec. 20, 1919; Jan. 10, 1920					
Age, 29	3/23/20	46	112	+48	1	Jan. 31, Feb. 21, 1920					
Duration,	3/27/20	44.5	88	+34	1	.....	.....	.....	.....	.....	No improvement; 5 roentgen rayings
1 year	4/ 9/20	44.5	80	+ 1	1	.....	.....	.....	.....	.....	On March 29, subtotal thyroidectomy
	10/23/20	55.5	84	0	2	.....	0	.....	0	.....	Much improved
	11/12/21	58.5	65	+ 3	3	.....	0	.....	0	.....	Clinically well
No. 485	1/14/20	52.5	90	+55	1	.....	+	+	+	Not + syst. mur.	Mild case
Mrs. J. L.	2/ 7/20	49.5	64	+18	1	Jan. 16, 1920					
Age, 29	2/11/20	49.5	56	+16	1	Feb. 9, 1920.....	.....	.....	.....	.....	Much improved
Duration,	4/29/20	63	52	—11	3	March 1, March 22, 1920...	.....	.....	.....	.....	Myxedema developed, started on thyroid
1 year	5/14/20	63.5	48	+ 1	1	.....	.....	.....	.....	.....	Better; thyroid stopped
	5/20/20	64	48	—11	1	.....	.....	.....	.....	Same	Myxedema again, started on thyroid
	6/19/20	64.5	52	+ 3	2						
	7/28/20	63.5	52	+10	2	.....	.....	.....	.....	.....	Thyroid stopped. Normal appearance
	9/28/20	62	52	+13	3	.....	0	0	0	.....	
	11/29/20	62	54	+11	3	.....	.....	.....	.....	.....	Clinically well
	5/ 5/21	62.5	60	+21	3						
	12/ 8/21	60.5	56	+11	3	.....	0	0	0	.....	Clinically well. Four months pregnant

No. 499	1/23/20	53.5	132	+53	2	.....	+	+	++	Normal	Moderately severe, getting worse
Mrs. N. B.	4/30/20	58.5	128	+46	2	Jan. 23, Feb. 16, Mar. 8, Mar. 29, 1920					
Age, 49	4/28/20	51.5	124	+39	2	Apr. 20, 1920.....	Less	Less	+	.....	Five roentgen rayings. Improved. Later operated and died
D., 18 mos.											
No. 559	3/25/20	67	120	+97	2	.....	++	++	+++	.....	Moderately severe. Stationary
Mr. W. S.	5/24/20	63.5	100	+76	2	Mar. 25, Apr. 14, May 4, 1920.....	.....	+	++	.....	Improved
Age, 27	6/14/20	70	84	....	2	May 24, 1920					
Duration,	7/ 7/20	73	92	+43	2	June 14, 1920.....	.....	Less	Less	.....	Much improved
1 year	9/15/20	74.5	72	+18	3	July 7, July 28, Aug. 25, 1920.....	Very slight	Same	Same	.....	Back at work. City fire department
	1/ 6/21	70	84	+51	3	.....	.....	.....	.....	.....	Work excessive last week
	2/10/21	68	84	+49	3						
	5/26/21	64	92	+17	3	Mar. 28, Apr. 18, May 9, 1921.....	Very slight	Very slight	0	.....	Clinically nearly well
	2/14/22	72	68	+37	3						
No. 566	4/ 2/20	42.5	94	+38	1	.....	Very slight	Very slight	++	Not +	Mild case
Mr. B. K.	7/24/20	47	72	+ 7	3	Apr. 10, May 1, 22, June 12, July 2, 1920..	Same	Same	+	syst. mur.	Much improved
Age, 42	10/ 1/20	49	88	+15	3	.....	.....	.....	.....	.....	Slight recurrence of symptoms
Duration,	1/12/21	51	72	+ 4	3						
5 years	12/15/21	55	62	− 8	3	.....	0	0	0	.....	Clinically well
	5/16/22	56	63	−13	3	.....	0	0	0	.....	Well except for hypertension
No. 575	4/ 8/20	61.5	112	+32	3	.....	++	++	+	Normal	Mild case
Mrs. R. H.	6/29/20	69.5	72	−15	3	Apr. 8, Apr. 26, May 17, June 7, 1920.....	+	+	0	.....	No hyper., suggestion of hypothyroidism
Age, 36	8/16/20	71	68	−20	3	.....	.....	.....	.....	.....	Clinically myxedema
Duration,	9/17/20	69	66	−13	3	.....	.....	.....	.....	.....	On thyroid, 3 gr. per day for 1 month
6 mos.	6/ 7/21	64	68	− 8	3	.....	.....	.....	.....	.....	No further treatment
	1/20/22	66	62	−11	3	.....	0	Very slight	0	Normal	Clinically well
No. 576	4/ 9/20	51.5	144	+60	2	.....	Very slight	+	++	Slightly +	Moderately severe
Mrs. K. C.	6/30/20	56.5	124	+49	2	Apr. 9, Apr. 30, May 21, June 11, 1920.....	.....	Less	+	.....	Somewhat better
Age, 28	8/16/20	61	124	+34	2	June 30, July 21, 1920					
Duration,	10/26/20	60.5	102	+31	2	Aug. 18, 1920.....	0	Same	+	.....	Much improved
6 mos	12/ 4/20	60.5	124	+45	2	.....	.....	.....	.....	Normal	
	2/ 3/21	58.5	114	+27	2	Jan. 19, 1921.....	.....	.....	.....	.....	Improvement continues
	4/ 2/21	56.5	106	+29	3	Feb. 9, Mar. 2, 1921					
	6/22/21	57	120	+53	3	Apr. 20, June 15, 1921					
	12/ 1/21	62.5	136	+40	3	July 6, 1921.....	+	Same	++	.....	Not so well
	1/21/22	60	121	+50	3	Dec. 1, Dec. 8, Dec. 21, 1921.....	Same	Same	++	Normal	Still thyrotoxic after 16 roentgen rayings
	2/ 9/22	58.5	102	+32	1	.....	.....	.....	.....	.....	Sent into hospital for operation
	2/13/22	58	114	+29	1						
	2/14/22	58	106	+28	1	.....	.....	.....	.....	.....	Operation postponed because of improvement without it
No. 577	4/ 9/20	50	118	+39	1	.....	++	0	++	Slightly +	Mild case without eye signs
Mrs. P. R.	4/17/20	48	100	+22	1	Apr. 12, 1920					
Age, 30	5/ 4/20	48	96	+20	1	May 3, 1920.....	+				
Duration,	9/15/20	57	78	+ 7	3	May 24, June 14, July 14, Aug. 4, 25, 1920	+	0	0	.....	Much improved
3 mos.	12/15/20	58	80	+ 6	3	.....	Very slight	0	0	Normal	Clinically not thyrotoxic
	3/10/21	52.5	88	+16	3						
	5/ 3/21	49.5	92	+17	3	.....	0	0	0	.....	Same. Some evidence of chr. nephritis
No. 591	4/22/20	46	102	+40	2	.....	++	Very slight	++	Not +	Moderately severe
Miss R. F.	6/25/20	48.5	80	+16	2	Apr. 22, Apr. 29, May 13, June 4, 1920.....	+	Less	+	syst. mur.	Improved
Age, 22	9/22/20	48	96	+13	3	.....	++	Same	++	.....	Not so well
Duration,	12/30/20	49	90	+26	3	.....	++	Same	++	.....	Same
3 mos	2/24/21	50.5	88	+23	3	Dec. 30, 1920; Jan. 19, Feb. 9, 1921.....	.....	.....	.....	.....	Subjectively better
	4/22/21	49	100	+18	3	Mar. 2, Mar. 30, Apr. 20, 1921					
	6/21/21	51	80	+25	3	May 25, June 15, 1921.....	.....	.....	.....	.....	Tonsillectomy 1 month ago

TABLE 1.—DATA ON EXOPHTHALMIC GOITER CASES—(*Continued*)

Lab. No.; Age; Duration of Disease	Date	Weight, Kg.	Pulse	Basal Metabolism, %	Activity	Roentgen-Ray Treatments Dates	Goiter	Exophthalmos	Tremor	Cardiac Condition	Remarks
No. 591— Cont.	10/28/21	52	98	+30	3	July 6, 1921	+	Less	+	.....	Still thyrotoxic. 13 roentgen rayings. Operation advised
	1/27/22	..	..	....	...	.....	.....	.....	.. ..	.....	Writes much improved following operation
No. 603 Miss M. M. Age, 21 Duration, 1 mo.	5/ 1/20	56	120	+68	3	.....	+	0	0	Not + syst. mur.	Clinically only mildly thyrotoxic
	5/14/20	57	132	+58	3	.....	.....	.....	+		
	5/28/20	54.5	118	+55	1	May 18, 1920	.....	.....	....	....	No improvement
	6/18/20	57	100	+35	1	June 8, 1920	.....	.....	.....	.....	Slight improvement
	7/20/20	58.5	112	+30	1	June 28, 1920	.....	.....	.....	.....	Worse. Much palpitation
	9/30/20	64.5	104	+24	2	July 21, Aug. 11, 1920					
	12/ 8/20	63.5	120	+59	2	Nov. 3, 1920	.....	.....	.....	.....	About the same condition
	12/18/20	61	130	+49	1	Dec. 22, 1920					
	1/12/21	62	122	+45	2	Jan. 12, Feb. 2, 1921					
	2/12/21	64	128	+52	2	Feb. 23, Mar. 16, 1921					
	3/21/21	66	120	+36	2	Apr. 6, 1921					
	4/27/21	66.5	112	+29	2	Apr. 27, 1921					
	5/14/21	65.5	108	+20	2						
	6/14/21	63.5	104	+26	2						
	8/ 3/21	65.5	104	+18	2						
	9/21/21	67	99	+21	2	June 15, July 6, 1921	0	0	++	.....	Tonsillectomy May 18
	10/25/21	66	102	+32	2	.....	.....	.....	.....	.....	Palpitation ++, otherwise feels well
	1/24/22	64.5	94	+31	2	.....	.....	.....	.....	Normal	Tachycardia and palpitation ++
	4/20/22	65	83	+12	3	Feb. 15, Mar. 8, Mar. 29, 1922	0	0	0	.....	Clinically well. Working
No. 621 Mrs. W. M. Age, 32 Duration, 10 mos.	5/20/20	56.5	120	+74	2	.....	++	+	+++	Not + syst. mur.	Moderately severe. Symptoms increasing
	6/ 9/20	57.5	110	+46	1						
	8/14/20	58.5	116	+50	2						
	9/16/20	58.5	96	+35	2	June 9, June 30, July 21, 1920	.....	.....	.....	.....	Subjectively better
	11/ 3/20	54	112	+66	2	Sept. 1, 1920	+	Less	++		
	12/ 3/20	53	104	+61	2	Sept. 22, Oct. 13, 1920	.....	.....	.....	.....	Not so well
	1/ 3/21	54	132	+61	2	Nov. 3, Nov. 24, 1920					
	2/ 5/21	54	120	+65	1	Dec. 15, 1920	.....	.....	.....	.....	Worse. 9 roentgen rayings to date
	2/18/21	54·	108	+48	1	.....	.....	.....	... ..	.....	On February 10, sup. arteries ligated
	3/ 5/21	52.5	112	+40	1						
	4/22/21	58.5	92	+13	1	.....	.....	.....	.....	....	On February 24, left hemithyroidectomy
	7/20/21	59	76	+ 9	3	.....	.....	.....	.....	.....	On April 14, partial right thyroidectomy
	10/20/21	58.5	71	+12	3	.....	.....	.....	.....	.....	Much improved
	5/11/22	55	75	+14	3	.....	0	0	0	Same	Clinically well
						.....	0	0	0	Same	Clinically well
No. 628 Mrs M. J. Age, 41 Duration, 10 years	5/27/20	49.5	120	+57	3	.....	++	+	+	Not + syst. mur.	Moderately severe
	11/16/20	48	106	+65	3	.....	.....	.....	.....		No treatment since first note
	1/ 3/21	48.5	122	+49	3	Nov. 17, Dec. 1, Dec. 22, 1920					
	2/ 2/21	50.5	108	+11	3	Jan. 12, 1921					
	3/23/21	53	94	+18	3	Feb. 2, Mar. 23, 1921	.....	.....	.....	. .....	Improved
	5/ 4/21	51.5	88	+ 9	3	Apr. 13, 1921					
	1/ 6/22	54	96	+15	3	June 28, 1921	+	Less	0	... .	Improved
	3/ 9/22	55	111	+22	3	.....	.....	.....	.....	... .	A little more palpitation
	4/14/22	55.5	90	+10	3	Mar. 14, Apr. 5, 1922	.....	.....	. ....	.....	Objectively improved
	5/17/22	55	67	—10	3	.....					

No. 657	6/22/20	66	96	+33	2	.....	+	+	+	Enlarged	Mild, but with thyroid heart
Mr. H. B.	7/ 3/20	65	104	+33	1	June 28, 1920				fibrillating	
Age, 43	10/ 6/20	66	100	+27	3	July 21, Aug. 11, 1920	Less	Less	0	Same	
Duration,	12/ 1/20	72	74	+20	3	Nov. 3, 1920					
4 mos.	1/ 6/21	72	84	+30	3	Dec. 1, 1920; Jan. 1, 1921	.....	.....	.....	.....	Thyroid symptoms nearly gone. Cardiac unchanged
	6/ 7/21	63	72	+34	3	Jan. 26, Feb. 16, 1921	.....	.....	.....	.....	On digitalis
	10/21/21	65	83	+41	3	.....	Very slight	Same	Slight	Same	On digitalis
	11/ 2/21	61.5	78	+40	1	.....	.....	.....	.....	.....	On digitalis
	11/ 5/21	61	71	+34	1	.....	.....	.....	.....	Same	Quinidin fails to restore normal rhythm
No. 728	9/16/20	65.5	110	+41	3	Aug. 18, 1920	+	+	+++	Not +	Moderately severe. Stationary
Miss B. M.	10/28/20	70.5	82	+19	3	Sept. 16, Oct. 7, 1920				syst. mur.	
Age, 39	1/13/21	76	80	+16	3	.....	+	Less	0	.....	Much improved
Duration,	3/31/21	72	100	+28	3	.....	Less	0	0	Normal	
10 mos.	5/12/21	77.5	70	+ 1	3	Mar. 31, Apr. 21, 1921					
	8/24/21	79	76	−11	3	.....	.....	.....	.....	.....	Clinically well
	1/26/22	81.5	78	+ 9	3	.....	0	0	0	Normal	Clinically well
No. 762	10/12/20	44	126	+67	1	.....	++	++	++	Normal	Moderately severe. Symptoms increasing
Mrs. M. H.	10/26/20	44	102	+47	1	Oct. 18, 1920					
Age, 28	11/ 9/20	46	100	+45	2	.....	+	+	++	.....	Slight improvement
Duration,	2/ 1/21	48.5	102	+42	2	Nov. 10, Dec. 10, 1920	.....	.....	.....	.....	Still thyrotoxic after 7 roentgen rayings
3 years	5/ 3/21	48.5	100	+37	2	Feb. 23, Mar. 16, Apr. 6, Apr. 27, 1921	.....	.....	.....	.....	On May 31, right hemithyroidectomy
	5/28/21	49	88	+31	1	.....	Left ++	+	++	.....	Still appears thyrotoxic
	6/10/21	48	96	+27	1	.....	Left larger	+	++	Slightly +	Worse. Two months pregnant. Second operation advised
	10/15/21	49.5	77	+15	2	.....	.....	.....	.....	.....	On February 10, partial left lobectomy
	1/19/22	50.5	96	+28	2	.....	.....	.....	.....	.....	Pregnancy continuing
	2/ 7/22	50	98	+31	1						
	2/17/22	49.5	99	+13	1						
	4/18/22	53	76	− 2	2						
No. 767	10/20/20	57	88	+41	2	.....	++	++	+++	.....	Moderately severe
Mrs. L. L.	2/ 3/21	61	82	+11	2	Oct. 20, Nov. 17, Dec. 15, 1920; Jan. 5, Feb. 2, 1921	++	+	++	.....	Much improved
Age, 48	3/ 2/21	61.5	88	+21	2						
Duration,	6/ 1/21	60.5	88	+23	3	Mar. 2, 1921					
1 year	8/ 3/21	63	88	+28	3	June 1, 1921	.....	.....	0	.....	Subjectively well
	1/23/22	..	..	....	...	.....	.....	.....	.....	.....	Writes that she is well
No. 780	10/29/20	49	120	+85	3	.....	++	+	++	Normal	
Mrs. E. M.	1/ 5/21	48.5	120	+64	3	Nov. 3, Nov. 24, Dec. 15, 1920					
Age, 35	3/23/21	..	...	+50	...	Jan. 5, Jan. 26, Feb. 16, 1921	.....	.....	.....	.....	Data supplied by Dr. Frank H. Lahey. He operated later
No. 798	11/19/20	63.5	120	+40	3	.....	+++	++	++	Normal	Moderately severe
Miss A. R.	1/19/21	61	96	+ 7	3	Nov. 19, Dec. 8, Dec. 29, 1920	+++	.....	+	.....	Much improved
Age, 17	3/ 3/21	61	78	+ 6	3	.....	+++	+	0	.....	
Duration,	4/14/21	60.5	110	+14	3	.....	++	.....	0	.....	Clinically well. Goiter still present
1 year	11/ 1/21	61	74	+ 8	3	May 4, 1921	+	Less	Very slight	.....	No symptoms except a little palpitation
	3/17/22	58.5	62	+ 4	3	.....	.....	.....	.....	.....	Essentially well
No. 802	11/15/20	68.5	124	+82	3	.....	++	++	++	Not +	Moderately severe
Mrs. F. S.	11/29/20	65.5	120	+75	1					syst. mur.	
Age, 26	1/24/21	71	96	+27	3	Nov. 30, Dec 22, 1920; Jan. 20, 1921	.....	.....	.....	.....	Improved
Duration,	3/16/21	74	84	+ 9	3	Feb. 9, 1921	+	+	0	.....	Much improved. Getting obese
18 mos.	7/21/21	72.5	104	+30	3						
	11/ 2/21	73	82	+ 3	3	.....	Less	Less	0	.....	Clinically well. Five months pregnant
	5/10/22	69.5	79	+10	3	.....	.....	.....	.....	.....	Clinically well. Normal delivery Mar. 27

TABLE 1.—DATA ON EXOPHTHALMIC GOITER CASES—(*Continued*)

Lab. No.; Age; Duration of Disease	Date	Weight, Kg.	Pulse	Basal Metabolism, %	Activity	Roentgen-Ray Treatments Dates	Goiter	Exophthalmos	Tremor	Cardiac Condition	Remarks
No. 803	11/16/20	71	112	+58	2	.....	+	+	+	Normal	Recent mild case
Miss P. S.	12/30/20	71	116	+51	2	Nov. 18, Dec. 9, Dec. 29, 1920.....	.....	.....	.....	.....	Slight improvement
Age, 35	3/ 2/21	74	98	+31	2	Jan. 20, Feb. 9, 1921.....	+	+	Less	.....	Slight improvement
Duration,	5/ 4/21	76.5	86	+10	2	Mar. 2, Mar. 24, Apr. 14, 1921.....	.....	Less	.....	.....	More improvement
6 mos.	11/ 7/21	80.5	90	+15	2	.....	0	Very slight	0	.....	Much improvement
	3/ 7/22	76	82	+10	3	.....	0	Very slight	0	Normal	Clinically well
No. 805	11/18/20	66.5	94	+24	2	.....	+	+	+	Slightly + syst. mur.	
Mrs. E. C.	1/31/21	66.5	112	+23	2	Dec. 8, Dec. 29, 1920; Jan. 19, 1921					
Age, 41	4/—/21	..	...	+12	...	Feb. 9, Mar. 2, 1921.....	.....	.....	.....	.....	On April 1, 1921; operation, Dr. Lahey
Duration,	2/ 6/22	..	...	....	...	.....	.....	.....	.....	.....	Writes that she is greatly improved
8 mos.											
No. 817	12/ 3/20	59	100	+47	2	.....	+	+	+	Enlarged	Mild case
Mr. E. B.	2/ 2/21	59	100	+54	2	Dec. 8, Dec. 29, 1920; Jan. 19, 1921.....	.....	Less	Less		
Age, 42	6/13/21	58	92	+53	2	Feb. 2, Mar. 16, June 8, 1921					
Duration,	10/10/21	56	74	+24	2	June 29, Aug. 17, Sept. 7, Oct. 5, 1921					
2 years	1/23/22	56.5	77	+30	2	.....	Less	Less	0	Normal	Symptoms much less marked
	4/26/22	54.5	91	+38	2						
	5/31/22	53.5	93	+35	2	Apr. 26, May 17, 1922					
No. 818	12/ 3/20	31.5	124	+81	1	.....	++	++	+++	Not + syst. mur.	Very toxic and acute case
Mrs. A. M.	4/18/21	42	100	+62	1	Dec. 15, '20; Jan. 6, 20, Feb. 9, Mar. 2, 23, '21					
Age, 46	5/26/21	45	106	+49	2	Apr. 23, May 11, 1921.....	.....	.....	.....	.....	Improved
Duration,	1/27/22	46	96	+44	3	June 1, June 22, Aug. 17, Sept. 28, 1921...	Less	+	+	Normal	Symptoms much less severe
8 mos.											
No. 819	12/ 4/20	60	100	+50	1	.....	++	+	+	Enlarged fibrillating	Partial thyroidectomy 7 years ago
Mrs. A. A.	12/14/20	60	100	+38	1	Dec. 8, 1920					
Age, 44	3/15/21	61.5	96	+ 6	2	Jan. 6, Jan. 26, Feb. 16, Mar. 9, 1921					
Duration,	6/ 4/21	64.5	76	+ 5	3	.....	.....	.....	.....	.....	Much improved
8 years	11/ 4/21	69	93	+31	3	.....	.....	.....	.....	Not so large normal rhythm	Not so well
	11/18/21	69	96	+32	3						
	1/25/22	70	66	− 6	3	Nov. 18, Dec. 7, 1921; Jan. 5, 1922.....	+	Very slight	0	Normal size and rhythm	Much improved

No. 866	1/25/21	51	120	+23	2	.....	+	+	0	Not + syst. mur.	Mild degree of hyperthyroidism
Miss M. K.	7/21/21	52.5	112	+37	1						
Age, 17	11/ 2/21	63.5	60	−15	2	Aug. 17, Sept. 21, 1921.....	+	+	.....	.....	Much improved. Suggests myxedema
Duration,	12/ 7/21	63	75	− 1	2						
1 year	2/19/22	57	91	+18	2	.....	.....	.....	.....	.....	Tonsillectomy on February 2
	3/24/22	56	86	+18	2	Feb. 25, Mar. 15, Apr. 26, 1922.....	.....	.....	.....	.....	Not so well. Considerable palpitation
No. 909	2/19/21	68.5	108	+22	2	.....	+	+	0	Enlarged	Hyperthyroidism slight. Goiter heart
Mrs. K. K.	4/ 2/21	67.5	118	+26	1						
Age, 23	4/11/21	64.5	108	+39	1	.....	.....	.....	.....	.....	No improvement on rest
Duration,	10/11/21	63	109	+38	2	.....	.....	.....	.....	.....	Roentgen ray treatment advised
5 years	12/16/21	65.5	72	+ 1	3	Oct. 19, Nov. 9, Nov. 23, Dec. 14, 1921.....	.....	.....	.....	.....	Much improved
	3/ 1/22	68.5	82	+ 4	3						
No. 933	3/16/21	58.5	100	+55	1	.....	+	+	+	Normal	Moderately severe
Mrs. C. S.	5/13/21	60.5	102	+47	2	Mar. 18, Apr. 13, May 4, 1921.....	.....	.....	.....	.....	Not much change
Age, 40						May 25, June 22					
Dur., 1 yr.											
No. 934	3/17/21	57.5	124	+73	2	.....	+	+	++	Slightly + syst. mur.	Moderately severe, acute case
Mrs. M. R.	5/23/21	55.5	122	+65	2	Mar. 30, Apr. 20, May 12, June 1, June 22					
Age, 34	10/19/21	58	117	+59	2	Aug. 17, Sept. 7, Sept. 28, 1921					
Duration,	11/30/21	58	121	+69	2	Oct. 19, Nov. 9, 1921; Jan. 4, 1922.....	+	+	++	.....	Slight improvement only. Operation advised
6 mos											
No. 937	3/18/21	48	134	+64	1	.....	++	++	+	Normal	Moderately severe, acute case
Miss M. H.	3/23/21	48	116	+46	1	Mar. 22, 1921					
Age, 23	6/15/21	54.5	92	− 2	2	Apr. 13, May 4, May 25, 1921					
Duration,	11/ 5/21	54	101	+13	3	.....	+	+	Very sligh	Normal	Much improved
6 mos	3/17/22	..	...	....	..	.....	.....	.....	.....	.....	Writes that she is "feeling fine."
No. 944	3/22/21	56.5	112	+58	2	.....	+	0	+	Normal	Moderately severe
Mrs. F. P.	8/ 2/21	54	100	+39	2	.....	.....	+	+		
Age, 45	9/15/21	59	119	+59	2	Aug. 6, Aug. 24, Sept. 14, 1921					
Dur., 1 yr.						Oct. 5, Oct. 26, Nov. 16, 1921.	.....	.....	.....	.....	No improvement. Operation advised
No. 967	3/31/21	50	124	+71	1	.....	++	+	+	Not + syst. mur.	Moderately severe
Mrs. F. A.	4/ 7/21	50	108	+49	1	Apr. 6, 1921					
Age, 30	6/15/21	55	96	+29	3	Apr. 27, May 18, June 8, 1921					
Duration,	10/28/21	57	87	+22	3	June 29, Aug. 17, Sept. 7, Sept. 28, 1921.	++	+	Very slight	.....	Much improved
1 year	1/ 6/22	56	104	+34	3						
	3/ 8/22	57	81	+15	3	Jan. 11, Feb. 1, Feb. 23, 1922.....	+	+	0	Normal	Much improved. Goiter and exophthalmos remain

TABLE 2.—DATA ON TOXIC ADENOMA CASES

Lab. No.; Age; Duration of Disease	Date	Weight, Kg.	Pulse	Basal Metabolism, %	Activity	Roentgen-Ray Treatments Dates	Goiter	Tremor	Cardiac Condition	Remarks
No. 26	6/22/15	60	97	+23	3	.....	0	0	Mitral disease	Diagnosis made of organic heart disease
Mrs. F. A.	4/ 9/19	59.5	107	+52	3	Feb. 27, Mar. 20, Oct. 29, 1918.....	.....	+	.....	Developed definite clin. signs of hyperthyroidism
Age, 33	2/26/.0	60	108	+28	3	Feb. 26, Mar. 22, Apr. 12, 1920	+	+	.....	Slight improvement
Duration, 6 mos.										
No. 313	8/13/19	40.5	113	+71	1	.....	Rt. + +	+	Normal	Moderately toxic
Miss V. G.	8/19/19	40	93	+66	1					
Age, 21	8/30/19	39.5	104	+48	1					
Duration,	11/24/19	40.5	92	+37	3	Sept. 15, Oct. 11, Nov. 3, 1919.....	.....	+		
4 mos.	12/ 1/19	40.5	90	+28	3	Nov. 24, 1919				
	3/15/20	41	92	+38	3	.....	.....	0	.....	Much improved
	12/ 2/21	..	..	....	3	Mar. 15, Apr. 5, Apr. 26, 1920.....	.....	.....	.....	Writes that she is well
No. 338	9/30/19	56	120	+63	1	.....	++	+	Normal	Moderately toxic, getting worse
Miss A. H.	10/ 8/19	55	104	+53	1					
Age, 32	11/10/19	58	100	+40	2	Oct. 8, Nov. 3, 1919				
Duration,	2/ 2/20	58	100	+32	2	Nov. 24, Dec. 15, 1919; Jan. 12, 1920.....	+	0	.....	Much improved
4 years	3/19/20	57	104	+34	2	Feb. 24, 1920				
	7/14/20	58.5	100	+27	3	Mar. 24, Apr. 14, May 5, 1920.....	+	+	.....	Much improved
	9/20/20	60.5	100	+24	3	.....	.....	.....	.....	On June 18, 1921, tonsillectomy
	4/27/21	56	100	+31	3					
	12/12/21	60.5	85	+17	3	.....	0	0	.....	Much improved
	3/14/22	60	86	+18	3	.....	0	0	Normal	Clinically well
No. 348	10/ 7/19	39	116	+50	3	.....	+	+++	Slightly + syst. mur.	Moderately toxic
Mrs. M. B.	12/15/19	42	100	+52	3	Oct. 7, Oct. 27, Nov. 19, 1919				
Age, 38	2/25/20	47	80	+18	3	Dec. 15, 1919; Jan. 5, Jan. 26, 1920.....	.....	0	.....	Much improved
Duration,	9/29/20	48.5	66	— 3	3	.....	.....	.....	.....	Clinically well
1 year	2/25/21	50.5	64	— 6	3	.....	.....	0	.....	Remained well. Skin a little dry
	8/29/21	48	40	—35	3	.....	0	0	.....	Became myxedematous. Started on thyroid
	9/15/21	45.5	61	+ 2	3	.....	.....	.....	.....	Returned to normal appearance on thyroid
	10/31/21	46	60	—13	3					
	1/10/22	46	63	— 1	3	.....	0	0	.....	Perfectly well. Continuing thyroid
	3/ 7/22	46	57	0	3	.....	.....	.....	.....	Perfectly well. Continuing thyroid
No. 440	12/ 8/19	53	105	+23	3	June 23, July 28, Aug. 19, Nov. 17, 1919...	+	+	Normal	Slightly toxic
Mrs. A. D.	3/16/20	53.5	96	+11	3	Dec. 8, Dec. 29, 1919.....	+	0		
Age, 39	2/ 3/22	54.5	87	+11	3	.....	Less	0	Normal	Clinically well
Duration, 3 years										
No. 456	12/20/19	46	118	+45	2	.....	+	+	Moderately +	Mild, stationary case. Adenoma removed 1 month ago. Hypertension
Mrs. J. F.										
Age, 52	3/13/20	48	120	+45	2	.....	.....	.....	.....	No treatment. No improvement
Duration,	6/ 3/20	48	120	+31	2	Apr. 1, Apr. 22, May 12, 1920				
2 years	8/ 2/20	46.5	110	+23	2	June 3, June 24, 1920				
	9/20/20	46.5	108	+15	2	Aug. 2, Aug. 23, 1920.....	.....	.....	.....	Clinically much improved
	2/ 4/22	46	106	+35	3	.....	0	0	.....	Slight return of nervousness
	5/ 5/22	46	93	+ 8	3	Mar. 3, Mar. 24, Apr. 14, 1922.....	.....	.....	Same	Moderate improvement

No. 633 Mrs. M. M. Age, 37 Duration, 2 years	6/ 2/20	51.5	119	+44	2		Rt., ++ Lt. +	+++	Normal	Slightly toxic
	7/27/20	52.5	116	+46	2	June 2, June 23, July 14, 1920				
	9/24/20	56	84	+23	2	Aug. 4, Sept. 1, 1920				
	12/ 6/20	53	102	+27	2	Nov. 17, Dec. 1, 1920	Same			
	1/20/21	57	120	+44	2	Dec. 23, Jan. 12, 1921				
	2/23/21	56.5	94	+22	2	Feb. 2, 1921	.....	.....	.....	Improved
	3/16/21	57.5	88	+12	2	Feb. 23, 1921	.....	.....	.....	Improved
	4/ 6/21	57	72	+10	3	Mar. 16, 1921				
	6/ 1/21	58	92	+10	3	Apr. 6, 1921	0	0	.....	Much improved
	10/ 5/21	62.5	81	+11	3		0	0	.....	Clinically well
	3/17/22	61.5	89	+15	3		0	0	Normal	Clinically well
No. 674 Miss M. G. Age, 45 D., 4 mos.	6/26/20	53.5	88	+29	2		++	+	Normal	Slightly toxic
	10/11/20	54.5	80	+ 5	2	July 1, July 26, Aug. 16, Sept. 20, 1920	.....	.....	.....	Some improvement
	2/ 2/22	57.5	62	−15	3		.....	.....	.....	Recurrence of symptoms. Feb. 18, 1921, hemithyroidectomy, Dr. G. W. W. Brewster. Now well
No. 704 Mr. O. S. Age, 27 D., 2 mos.	7/24/20	57.5	94	+29	3		+	++	Normal	Slightly toxic
	12/19/21	61.5	66	+ 5	3	July 28, Aug. 18, 1920	0	0	.....	Clinically well
	5/ 9/22	55	104	+52	...	May 31, 1922	+	++	.....	Definite relapse. Return of symptoms
No. 716 Mrs. A. M. Age, 50 Dur., 3 yrs.	8/ 9/20	50	130	+47	3		Rt. +	+	Slightly + syst. mur	Slightly toxic
	10/ 4/20	53	128	+36	3	Aug. 9, Aug. 26, Sept. 15, 1920				
	11/ 3/20	52	108	+16	3	Oct. 5, 1920				
	10/ 5/21	54.5	104	+22	3	Nov. 3, 1920	.....	.....	.....	Much improved
No. 734 Mrs. M. D. Age, 40 Duration, 1 year	9/18/20	45	100	+48	1		+	+	Normal	Moderately toxic
	10/ 2/20	43	98	+41	1	Sept. 24, 1920				
	10/25/20	44	92	+45	1	Oct. 14				
	11/ 5/20	45	100	+42	2	Nov. 3				
	12/15/20	52	120	+44	3	Nov. 24	.....	.....	.....	Much improved
	1/ 5/21	53.5	112	+44	3	Dec. 15				
	1/26/21	56	100	+37	3	Jan. 5, 1921				
	2/16/21	57	100	+27	3	Jan. 26, 1921				
	3/16/21	58	97	+24	3	Feb. 16	.....	.....	.....	Improvement continues. Getting obese
	5/18/21	58	92	+14	3	Mar. 16, Apr. 6, Apr. 27, 1921				
	8/26/21	62	70	− 1	3		0	0	.....	Clinically well
	12/21/21	66	85	+10	3		0	0	Normal	Clinically well
No. 738 Mrs. M. S. Age, 48 Duration, 3 years	9/23/20	49.5	100	+22	2		Lt. +	+	Slightly +	Slightly toxic
	12/ 3/20	51.5	80	+24	2	Oct. 6, Oct. 27, Nov. 24, 1920				
	1/19/21	52	74	+14	2	Dec. 15, 1920				
	3/ 9/21	52.5	72	+20	2					
	8/17/21	49	64	+17	2	May 11, 1921	Nearly gone	0	.....	Much improved
No. 867 Miss A. G. Age, 55 Duration, 6 mos.	1/25/21	48.5	92	+45	2		+	+	Enlarged	Moderately toxic. Cardiorenal as well
	3/23/21	47.5	88	+37	2	Feb. 9, Mar. 2, 1921				
	6/15/21	56	76	+ 5	2	Mar. 23, April 13, May 25, 1921				
	8/17/21	58.5	84	+15	2		0	0	.....	Not well; trouble, cardiac chiefly
No. 964 Mrs. M. M. Age, 52 Duration, 7 years	3/29/21	51	120	+66	1		Rt. +	+	Enlarged and fibrillating	Marked goiter heart
	3/31/21	51	112	+45	1					
	11/ 5/21	53	100	+43	2	Apr. 6, Aug. 25, Sept. 14, Oct. 5, 25, 1921	Same	+	Same	Thyroid symptoms less, cardiac same
	1/ 3/22	56	102	+30	2	Nov. 16, Dec. 7, Dec. 28, 1921	Same	.....	Same	Same
	2/15/22	56	89	+35	...	Jan. 17, 1922				
	5/ 2/22	56	81	+ 9	...	Feb. 15, Mar. 15, Apr. 12, 1922				

This chart is made in a somewhat peculiar way. We wished to get all available cases into the early portion of the curve, but it will be noted that some drop out from time to time, so that fewer cases were used in the later than in the earlier portion of the curve.

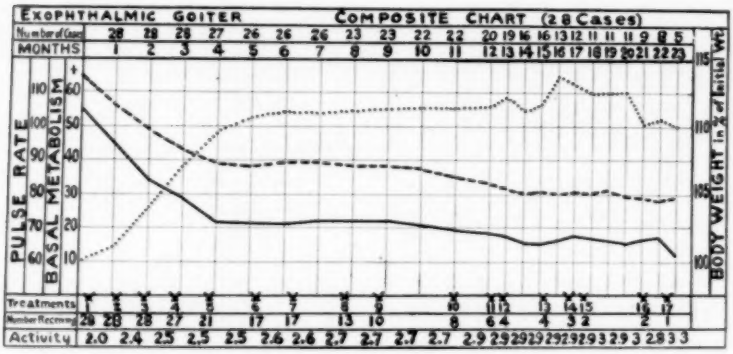

Fig. 1.—In this and in all the other charts, the perpendicular rulings are at intervals of one month. The solid black line denotes basal metabolism (per cent. variation from Sage Institute standards), the interrupted line represents the pulse rate, and the dotted line represents body weight. In Figures 1 to 5 the weight is expressed in per cent. of the initial weight which is taken as 100 per cent. Figures 1 to 5 are composite, the remaining figures are individual charts. Roentgen-ray treatments are denoted by X. Activity in Figures 1 to 5 is shown in the following manner: 1, denotes complete rest in bed; 2, partial rest; 3, following usual occupation. For the composites these figures for all individuals composing the composite are averaged.

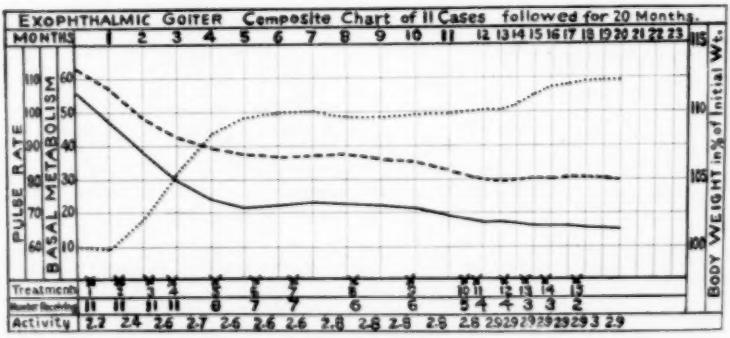

Figure 2.

To answer what might be an objection to this method of charting, we have in Figure 2 shown the composites of the eleven cases in which our data run through twenty months. It is interesting to note that this chart is nearly identical with the first. The drop in this instance in

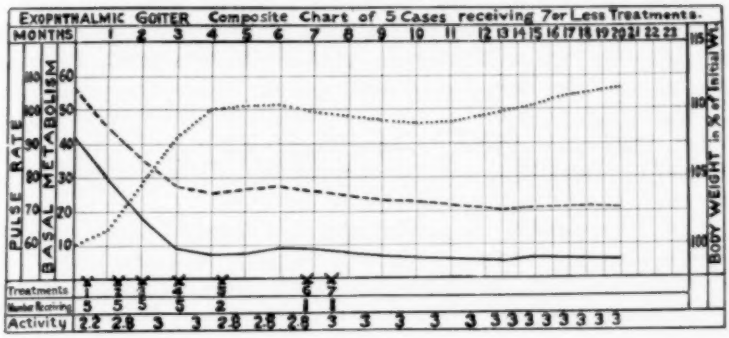

Figure 3.

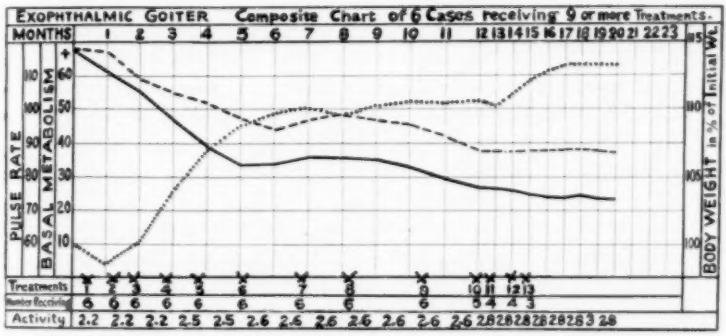

Figure 4.

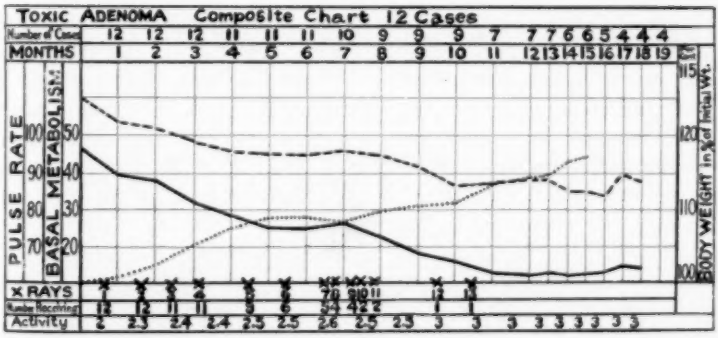

Figure 5.

four months is in the pulse, from 113 to 89, and in the metabolism, from + 56 to + 24 per cent. The weight increase was 8 per cent. A further drop of 2 or 3 points occurred in the fifth month, and then there is the same plateau seen in Figure 1.

To get some idea of the relation of the number of treatments to the effect, we have separated the cases shown in Figure 2 into a group (Fig. 3) of patients receiving seven treatments or less, and those (Fig. 4) receiving nine treatments or more.

Both these charts are similar in general contour to the previous ones. The cases averaged in Figure 3, receiving the smaller number of treatments, are not unnaturally the milder ones. In this group the pulse and metabolism both assume normal levels at the end of four months, the former falling from 107 to 75 and the latter from + 43 to + 7 per cent. Furthermore, they stay at these normal levels through the twentieth month.

In the more severe group, shown in Figure 4 and receiving more treatment, there are similar drops in pulse and metabolism curves and rise in the weight curve. The drops in the first two, however, do not bring them by any means to a normal level; the pulse falls from 118 to 97 and the metabolism from + 68 to + 34 per cent. in the first five months. From then on, through the next fifteen months, there is only a further drop of 10 points in pulse and metabolism in spite of continued roentgen-ray treatment.

Recent Series: *Toxic Adenoma.*—Turning now to the cases of toxic adenoma we find that all the patients showed improvement with roentgen-ray therapy and five were apparently cured. The composite curves are shown in Figure 5.[37] The character of the curves is quite different from that of the exophthalmic goiter patients. The drop in pulse and metabolism is far more gradual. So, too, is the gain in weight. Nevertheless, in the group as a whole a normal pulse and metabolism level is finally reached.

Prewar Series: *Exophthalmic Goiter.*—In the report published in 1919 by Means and Aub [3] were given the data on fifteen patients with exophthalmic goiter treated by roentgen ray alone. We have attempted to get end result data in all of these cases. Three patients have been lost, three have died; the remaining nine have been to the laboratory this spring (1922).

A summary of the data already published for these, together with the data just received, is given in Table 3.

It will be noted that six of the nine patients have normal metabolic rates five or six years after their first treatment; another has a slight

37. Two cases in Table 2 are not included in the composite because of insufficient data (Cases 26 and 440).

elevation, + 15 per cent. She, however, had no clinical symptoms or signs and like the six with normal rates was apparently in good health. Two others still had elevated metabolism and clinically were better but not well. Both patients had been advised to submit to an operation in 1919 but had refused.

V. ILLUSTRATIVE CASES

We have previously emphasized the importance of the chart in following the progress of toxic goiter or myxedema,[2, 31] and pointed out that with the patient with thyroid disease the clinical chart serves the same purpose that it does in the fever patient. In thyroid disease, however, we plot not pulse, temperature and respiration, but metabolism, pulse and weight.

TABLE 3.—DATA ON CASES PREVIOUSLY PUBLISHED

Laboratory Number	Number of Roentgen Ray Treatments	Date of First Treatment	Date of Last Treatment	Basal Metabolism						
				Basal Metabolism Before Treatment	One Year After First Treatment	Two Years After First Treatment	Three Years After First Treatment	Four Years After First Treatment	Five Years After First Treatment	First Treatment Six Years After
12. Mrs. T. W.	6	1/26/16	8/31/16	+71, +49	+46	....	....	....	....	+40
25. Mrs. A. L.	14	6/24/15	2/15/18	+83	+61	+63	....	+14	....	+ 4
33. Mr. B. S.	6	10/13/15	7/ 5/16	+78	+14	....	—14	....	....	— 1
48. Mrs. E. N.	13	1/12/16	11/ 3/17	+82	+54	....	+27	....	....	+15
53. Mr. R. S.	7	2/16/16	6/ 6/16	+48	+49	+13	....	+16	+ 7	0
66. Miss E. C. C. ..	11	8/29/16	7/ 7/17	+42	+28	— 6	....	....	— 5	
110. Miss S. E. M. ..	6	11/28/16	3/30/17	+34, +42	— 1	+15	....	....	+ 8	
122. Mrs. C. M.	6	1/ 2/17	5/ 5/17	+89, +74	+66	+39	....	+43	+35	
135. Mrs. V. M. D. ..	7	4/ 2/17	1/ 3/18	+39, +22 +28, +47	+25	+ 4	....	....	— 5	

We cannot conveniently give the charts of the fifty-eight cases in the present series; certain of them have appeared elsewhere,[2, 4, 6, 31] others we will give now, and for the remainder the reader is referred to Tables 1 and 2, which contain all the essential data, though not in graphic form.

The charts shown here are chosen to illustrate certain type reactions and special points.

We will discuss, first, the findings in three patients who responded very favorably to roentgen-ray therapy.

REPORT OF CASES

CASE 376.—Mrs. R. N., a Jewess, aged 27, had had toxic symptoms for one year and a goiter for four months. The symptoms began after an attack of influenza. She had had no treatment previous to her first visit to the hospital. She had slight, but definite, eye signs, slight soft symmetric enlargement of the thyroid with bruit, and a slight tremor. It was felt that she had typical but

not more than moderately severe exophthalmic goiter. She has received no treatment except nine irradiations. She has even kept at her usual mode of life—housewife—and has done her work as usual.

Her chart is shown in Figure 6. Her metabolism began to drop after four treatments and reached normal after nine. The curve stayed at the normal level for the next eighteen months, and she has been relieved of all symptoms. To date, it seems to be a complete cure.

Case 803.—Miss P. S., graduate nurse, aged 35. Trouble began six months before we saw her. After getting very tired physically, she developed palpitation, marked asthenia and weight loss. She had slight but definite eye signs, slight fulness of the thyroid without bruit, slight but definite tremor and warm moist hands. A diagnosis of exophthalmic goiter was made and she was started on roentgen-ray treatment. The chart is shown in Figure 7. She gave up her work for the greater part of a year, but in other respects was reasonably active. The only treatment was the roentgen-ray. As the chart shows, metabolism and pulse

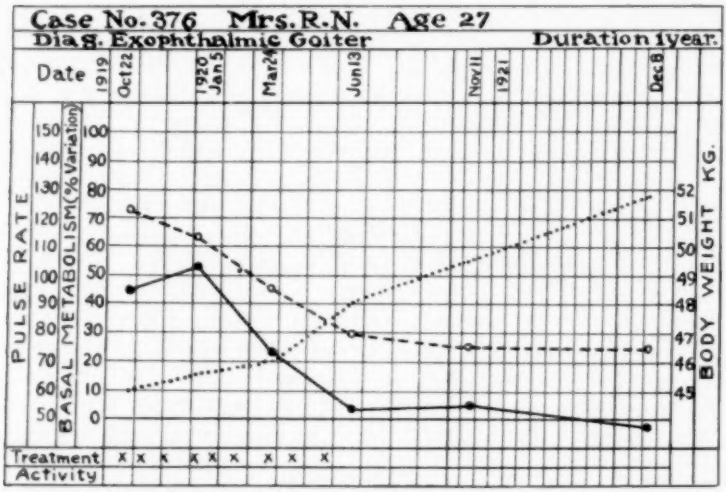

Fig. 6.—This chart and Figures 7 to 14 inclusive are constructed like the preceding composites, except that body weight is given in kilograms, and activity is shown by shading instead of by numbers; full black = rest in bed, half black = partial rest, all white = usual mode of life.

curves reached an essentially normal level in six months and have stayed so for ten months more. She has been back at work for four months without ill effect. Her work is caring for a psychopathic patient and is not easy.

Case 802.—Mrs. F. S., a Jewess, aged 26, who for eighteen months had exophthalmos, thyroid enlargement and the classical symptoms of hyperthyroidism. She had had no treatment when we first saw her. A diagnosis was made of exophthalmic goiter of moderate severity, and a course of roentgen-ray treatment prescribed. She came into the hospital for a fortnight. Her roentgen-ray treatment was started and then she went home and led her usual life. The chart (Fig. 8) shows a rapid fall in metabolism and pulse, reaching normal in four months, and a marked gain in weight. The high result of July 21, 1921, was at a time when she was starting a pregnancy. Seen again Nov. 2, 1921, she was five months pregnant, her metabolism was normal, and everything was going smoothly. We heard from her when nearly full term (March 15, 1922),

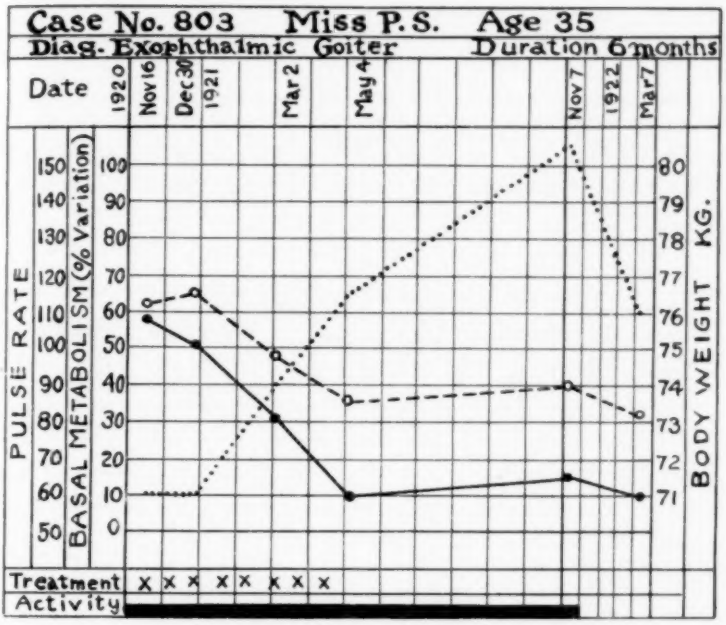

Fig. 7.—The solid line indicates basal metabolism; interrupted line, pulse rate; dotted line, body weight. Activity is shown by shading; solid black squares indicate rest in bed; half black squares, partial rest; white squares, usual mode of life.

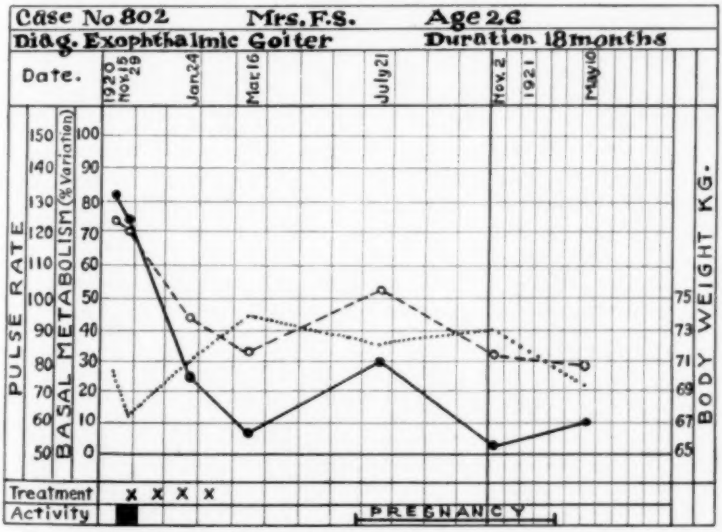

Fig. 8.—The solid line indicates basal metabolism; interrupted line pulse rate; dotted line, body weight. Activity is shown by shading; solid black squares indicate rest in bed; half black squares, partial rest; white squares, usual mode of life.

and there were still no symptoms referable to hyperthyroidism. Her baby was born at full term on March 27; normal delivery. On May 10 she was clinically well and had a normal metabolism.

The next three cases illustrate improvement under roentgen-ray treatment followed by relapse. The first portion of the story and the charts of two of the patients were published a year ago (June, 1921).[31] The events which have occurred since then in each case are instructive and make it seem worth while to republish the charts, bringing them up to date.

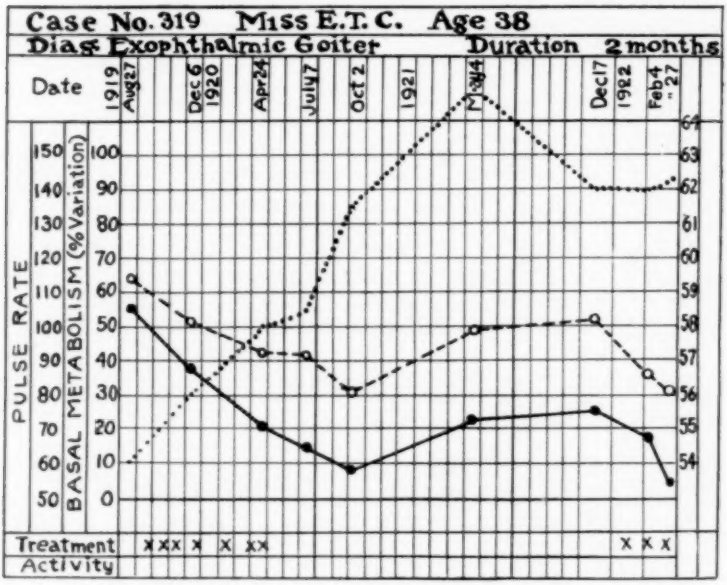

Fig. 9.—The solid line indicates basal metabolism; interrupted line, pulse rate; dotted line, body weight. Activity is shown by shading; solid black squares indicate rest in bed; half black squares, partial rest; white squares, usual mode of life.

Case 319.—Miss E. T. C., aged 38, with a recent and mild form of exophthalmic goiter. The chart as shown a year ago showed a steady improvement and return to normal under roentgen-ray treatment alone up to the fourteenth month. An observation in the twenty-first month, however, showed a rise. The remark was then made, "This rise may or may not be of importance. But it illustrates . . . . . the usefulness of the chart, for it puts us on our guard against a possible relapse which we might have missed on the basis of the clinical picture alone," for there were no symptoms at that time. The chart given now (Fig. 9) shows that the relapse did materialize, though it was a mild one, and that it is again being controlled by roentgen-ray treatments.

Case 603.—Miss M. M. The chart of this patient when first published showed the events of a year. Now we add a second year. This patient has

always been somewhat atypical, probably a case of exophthalmic goiter, but never showing any eye signs. She responded well to roentgen-ray treatment but relapsed. Last year the remark was made, "A second course of roentgen-ray treatment seems to be relieving this (relapse) much as it did in the first instance." This statement proved to be unduly optimistic, as is shown in Figure 10. A third course of treatment was necessary, but seemed to have the desired effect. She is at last apparently well and has been working for three months.

Case 411.—Mr. A. S., a business man, aged 39 years, showed a rapid improvement with roentgen-ray and then a slight relapse. In November, 1919, he consulted Dr. Edsall, who found that he had typical exophthalmic goiter of moderate severity. The symptoms had been present for but three months at that time. His chart is shown in Figure 11. After the third roentgen-ray treatment he showed a marked clinical improvement, fall in pulse and metabolism and gain in weight. When seen Oct. 22, 1920, he had a slight return of symptoms and an elevation in metabolism. This observation was obtained,

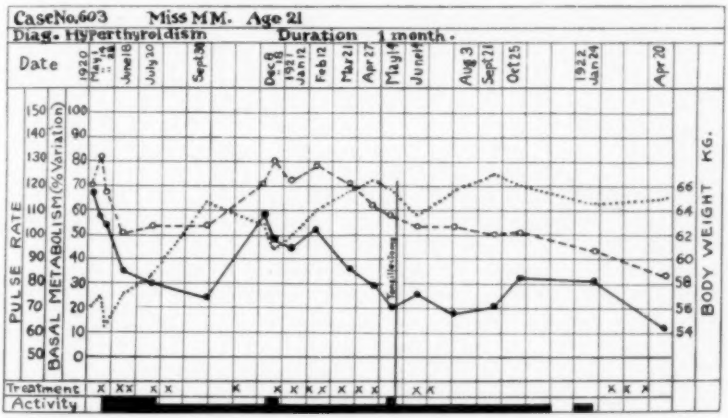

Fig. 10.—The solid line indicates basal metabolism; interrupted line, pulse rate; dotted line, body weight. Activity is shown by shading; solid black squares indicate rest in bed; half black squares, partial rest; white squares, usual mode of life.

however, at the end of a spell of very hot weather which had used him up a good deal. Jan. 15, 1921, after two more roentgen-ray treatments, he was much better and had returned to work. May 1, 1921, there was again an increase in metabolism and slight return of symptoms. This was during hot spring weather. The last observation was made April 29, 1922. He had worked all winter and considered himself well, except that he still gets tired rather easily. The exophthalmos, the goiter and the tremor had disappeared, and the heart was normal.

Case 591.—Miss R. F., aged 22, with a recent (three months) and mild type of exophthalmic goiter, showed no consistent improvement with the roentgen-ray. Her chart is shown in Figure 12. A slight drop in pulse and metabolism and slight gain in weight, together with a little symptomatic improvement, occurred after four rayings, but at the end of the eighteen months she was no better than at the start, although she had had a total of thirteen treatments. This was a definite failure of roentgen-ray treatments. We advised her to have an operation and she went to Dr. Frank H. Lahey,

who operated. Jan. 27, 1922, she wrote us that she was very much improved following the operation.

Case 633.—Mrs. M. M., aged 37, had an adenomatous goiter with hyperthyroidism. She had had symptoms of hyperthyroidism for two years when we first saw her. Her chart (Fig. 13), shows that a first course of treatment caused some improvement. Then there was a slight relapse, but a second course brought about an essentially normal state and at the same time the goiter disappeared.

Of the prewar series there are two cases in which the recent events are sufficiently interesting to deserve individual note. The early histories of both of these have already been published.[3]

Case 48.—Mrs. E. N., aged 30, had had exophthalmic goiter for four and a half years when she first came to us. The chart as originally published shows a drop in metabolism of about 20 points coincident with rest in bed and the

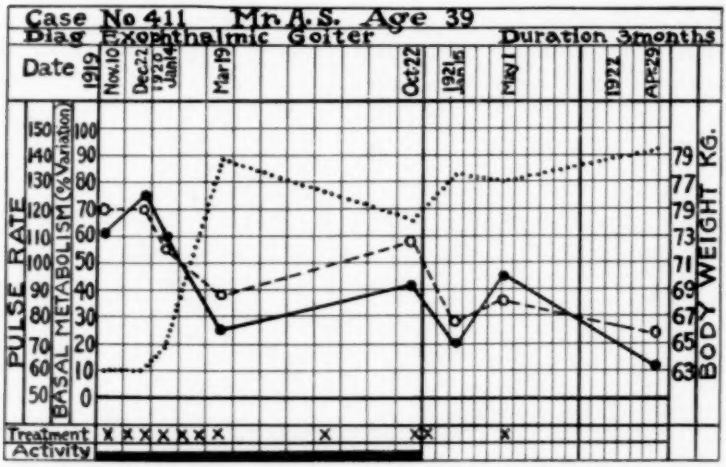

Fig. 11.—The solid line indicates basal metabolism; interrupted line, pulse rate; dotted line, body weight. Activity is shown by shading; solid black squares indicate rest in bed; half black squares, partial rest; white squares, usual mode of life.

first two roentgen-ray treatments. There was then a period of four months in which there was no treatment but partial rest. She gained some weight and her pulse fell somewhat, but her metabolism showed no drop. She resumed her work (housewife, family consisted of husband, two children, sister and sister's child). After four months of this a further gain in weight but no change in metabolism and a slight gain in pulse. More vigorous roentgen-ray treatment was then started and with no other change there was a gradual improvement, with fall in pulse and metabolism which extended over a period of six months. Two years later she was clinically much better but with a metabolism elevation of + 25 per cent. She reported again in December, 1921, in response to a letter. The metabolism now was + 15 per cent. and she was clinically well. The most interesting feature of this case is the prompt fall in metabolism and pulse coinciding with the resumption of roentgen-ray treatment.

Case 33.—Mr. B. S., was a Jewish barber, aged 24. The last published note in his case is as follows: "This case illustrates as well as any we have, a

very toxic type of exophthalmic goiter, with steady improvement and ultimate complete recovery following essentially no therapy whatever beyond six roentgen-ray treatments." The events subsequent to the time this note was made (May, 1919) are interesting.

May 16, 1921, he reported of his own accord and said that for six months he had been feeling weak and rather dopey, though he had kept at his work. The clinical picture was the classical one of myxedema. The metabolism was —20 per cent. He was started on thyroid, which quickly controlled the symptoms and brought the metabolism to a normal level. The progress and dosage of thyroid is shown in the chart. The last observation which shows a drop to —15 per cent. was after he had been off thyroid for about ten days because of his being in the Massachusetts Charitable Eye and Ear Infirmary for the removal of a small fibroid tumor of the vocal cord.

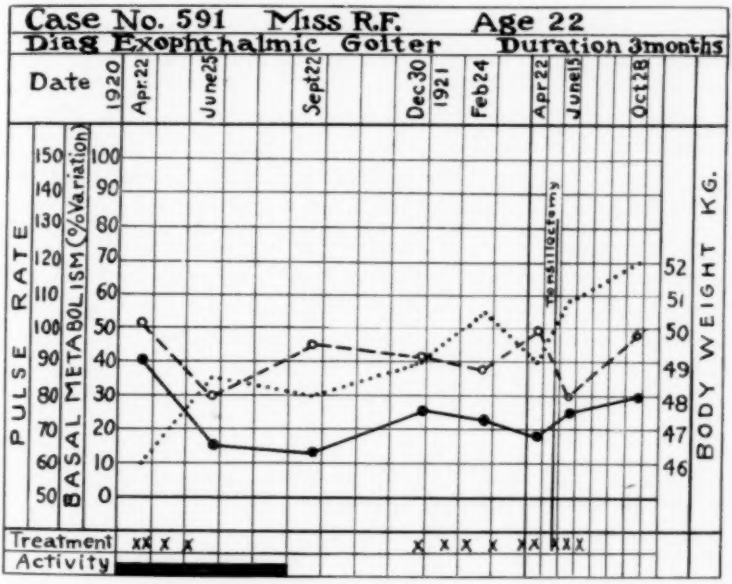

Fig. 12.—The solid line indicates basal metabolism; interrupted line, pulse rate, dotted line, body weight. Activity is shown by shading; solid black squares indicate rest in bed; half black squares, partial rest; white squares, usual mode of life.

VI. DISCUSSION

The objects we had in mind in undertaking this research were to find out whether roentgen-ray therapy in toxic goiter did any good or harm, and, if the former, whether it works in all cases, what the manner of its action is and whether the effect is permanent; also to discover if possible in what types of cases it worked best, provided any evidence was secured of its working at all.

The data presented here, we believe, throw light on some of these problems. In the first place, in the recent series there were two out

of three patients with exophthalmic goiter who showed a noteworthy fall in pulse and metabolism coincident with exposure of their thyroid and thymus glands to the roentgen ray. This has led us to believe that in these cases the roentgen ray had a beneficial effect. Plummer [38] has objected to this conclusion on the basis that the natural course of exophthalmic goiter is a most uneven one and that improvements and relapses may occur at any time spontaneously. Therefore, he felt that our data proved nothing regarding the effect of the roentgen ray. He may be right. He remarked, and we deplore, the lack of control cases.

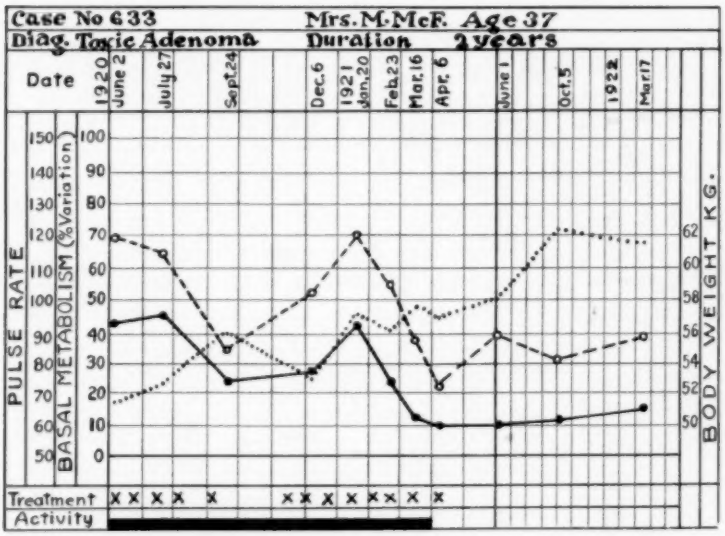

Fig. 13.—The solid line indicates basal metabolism; interrupted line, pulse rate; dotted line, body weight. Activity is shown by shading; solid black squares indicate rest in bed; half black squares, partial rest; white squares, usual mode of life.

But until someone produces a satisfactory experimental exophthalmic goiter, controls will only be secured by chance. It is not permissible deliberately to withhold treatment from a group of patients with exophthalmic goiter for the sole purpose of accumulating scientific facts, nor would any but the very exceptional patient permit it should the attempt be made.

Until the study of exophthalmic goiter can be made experimentally, then, we shall have to get along without untreated controls, and glear

38. Plummer, H. S.: In discussion of present paper when it was read in abstract before Association of American Physicians, May, 1922. Tr. Ass. Am. Phys., 1922.

what information we can by the methods open to us. This difficulty applies to the study of many clinical problems. It is by no means confined to exophthalmic goiter. Does the dietetic treatment of peptic ulcer do any good? Nobody knows in Plummer's sense. Patients with peptic ulcer get well with no treatment sometimes, just as exophthalmic goiter patients undoubtedly do in some instances.

If we accept the theory that the symptoms manifested in hyperthyroidism are due to increased activity of the cells composing the thyroid

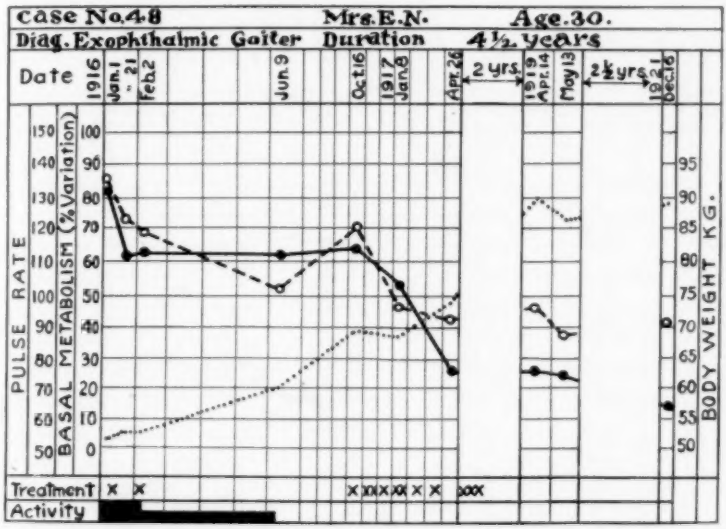

Fig. 14.—The solid line indicates basal metabolism; interrupted line, pulse rate; dotted line, body weight. Activity is shown by shading; solid black squares indicate rest in bed; half black squares, partial rest; white squares, usual mode of life.

gland, then the application of any method of treatment which is known to inhibit or destroy cell function would be rational.

What, if any, evidence have we that in the roentgen ray we have such an agent?

It has been repeatedly shown by laboratory investigations that if a living organism be exposed to irradiation, retardation of growth, inhibition of function and death to the organism will take place, and that this change will be dependent on the amount of radiation absorbed, the character of the cells rayed, and the conditions to which they are subjected before and after irradiation.

Schwartz [39] found that if he radiated dry vegetable seeds no variation whatever from the normal could be produced in the development of the plant. The cells of the germ in the dried state, with their metabolism reduced to a minimum, are not affected by irradiation. But, if through the addition of water the metabolism is stimulated and the seed germinates, it then becomes highly sensitive to radiation. This sensitiveness of the cell is in proportion to its metabolism. He also found that the sensitiveness of the plant diminishes with increase in age, and is slightly, if at all, affected at maturity. Similar experiments with lower forms of animal life have given similar results. From investigations of this kind and his own studies Bergonie was able to

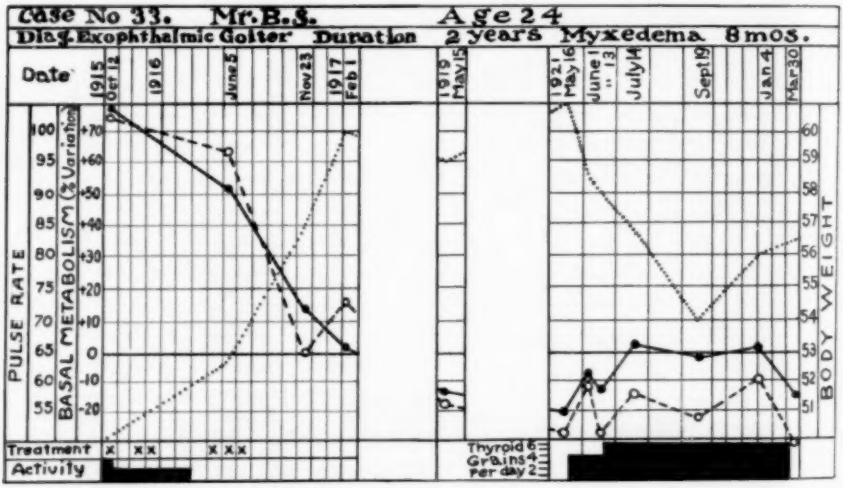

Fig. 15.—In the right hand portion the dose of thyroid given during the period of myxedema is shown by width of shading.

formulate laws governing the sensitiveness of cells to radiation, and he states that the roentgen ray acts more intensively on the cell the greater its reproductive capacity, the longer its karyokinetic stage and the less its morphology and its function, except the power of reproduction, are definitely fixed. The first of these laws is by far the most important. All active cells are highly sensitive to radiation. Every cell of whatever kind it may be becomes less resistant to radiation as soon as it becomes active.

39. Schwartz: Quoted by Wetterer, L., in Handbuch der Röntgen und Radium Therapie **1**:373, 1919.

In the field of clinical investigation, there is also abundant evidence that glandular function is especially sensitive to radiation. About one-fifth of the dose necessary to produce slight reddening of the skin if absorbed by the ovaries will cause cessation of the menstrual flow, and a similar dose to the testicles will cause the disappearance of the spermatozoa from the seminal fluid. A dose well below that, sufficient to cause injury to the skin, will stop the flow of saliva from the parotid gland. Slightly larger or repeated doses will cause any of these glands to become permanently atrophied. Furthermore, it has been observed that there is an increased sensitiveness in certain tissues in the young which lose their sensitiveness in the adult. Also, an increased sensitiveness may occur in tissues formerly less sensitive as soon as they begin to proliferate, as for example, the sensitiveness of the lacteal gland at the beginning of pregnancy compared with its low sensitiveness before conception, or at the height of its development.

From these observations, taken from many fields of investigation, it would seem that we have ample justification for supposing that the hyperactive thyroid would be favorably affected by radiation, and that this effect could be obtained with a dose well below that sufficient to cause injury to the overlying skin. It also becomes evident why the normal gland tolerates a much larger amount of radiation than the pathologically active one, and explains the failure to produce myxedema in animals except when using doses large enough to produce definite injuries to the glands and surrounding tissues.

From the clinical point of view we believe that data of the sort we have presented here are very highly suggestive, if not positive proof, of a beneficial effect of the roentgen ray in the majority of cases of exophthalmic goiter. It would be a very remarkable coincidence if we chanced to start roentgen-ray treatment in two out of three cases just as they were about to begin a rapid spontaneous drop. It is possible, but not probable. One can say positively, at any rate, that in two out of three of our cases there was improvement coincident with the inauguration of roentgen-ray treatment.

The rapidity of the drop is greater in the recent than in the prewar series. This very likely is due to incomplete dosage in certain cases of the earlier series, and sometimes to greater intervals between treatments.

If the roentgen ray has an effect, and if it fails to act in certain cases, the next problem becomes one of finding the type of case that will respond or fail to respond. With this in view we have made a survey of the severity, duration and age of the forty-four patients with

exophthalmic goiter who comprise our recent series. The average age, duration and metabolism (before treatment) of several subgroups is shown in Table 4.

This table would seem to indicate that neither the age of the patient nor the intensity of the hyperthyroidism as shown by the level of the metabolism is a factor in determining the success or lack of success of roentgen-ray treatment. The average length of the disease in the group that showed improvement was about seven months greater than that of the group that showed no improvement. It might be argued, therefore, that the former were more nearly at the point when spontaneous recovery might be expected to occur than the latter. The duration of exophthalmic goiter is given by different authors as from six months to several years. Cases running a spontaneously abortive course lasting but a few months may occur, but they are not the rule. It is also worthy of note that out of the twenty-eight improved cases there were eight in which the disease had lasted but six months or less

TABLE 4.—AVERAGES FOR EXOPHTHALMIC GOITER PATIENTS

Cases	Basal Metabolism			Duration of Disease, Years			Age of Patient		
	Average	Maximum	Minimum	Average	Maximum	Minimum	Average	Maximum	Minimum
16 unimproved	59	85	21	1.4	3.0	0.2	36	62	22
28 improved	55	97	32	2.0	10.0	0.1	34	53	17
12 recovered*	51	85	22	2.0	5.0	0.5	33	53	17
7 relapsing*	61	97	37	1.5	8.0	0.1	30	44	17

* Included in the group of 28 improved cases.

at the time roentgen-ray treatment was started. In spite of the short duration of the disease, they all showed a definite drop with the roentgen ray, nor were they cases of a particularly mild type—the average metabolism of the group before treatment being + 55 per cent. and four months later + 17 per cent. If the improvement following roentgen-ray treatment is not the result of the treatment but the mere natural course of the disease, one would expect to find certain cases getting progressively worse during treatment, but, as a matter of fact, we do not find such.

Another point which is strongly suggestive that the roentgen ray has a definite action on the thyroid is the development of myxedema. Two of our exophthalmic goiter patients, as has been reported elsewhere,[31] developed the classical picture of myxedema within the first four months of vigorous roentgen-ray treatment. Both were restored to normal levels by thyroid and in both thyroid was later discontinued without a return of the symptoms. Their thyroids were temporarily depressed apparently, not permanently as in spontaneous myxedema.

Another patient developed myxedema eighteen months after roentgen-ray treatment. This was a case of toxic adenoma. A fourth developed it five years after. It is more difficult to ascribe the effect in the last two cases to the roentgen ray, but the first two cases are highly suggestive.

While untreated control cases are lacking in this series, we have in a few cases a control period. That is to say, metabolism observations were secured over a considerable period before roentgen-ray treatment was started. This occurred in Cases 48, 456, 628 and 909. In each of these, directly coincident with roentgen-ray treatment, there was a rapid improvement, although they had been stationary before, and with the addition of no new factor but the roentgen ray. This evidence, too, we believe suggests strongly that the roentgen ray has an effect.

The results of treatment of exophthalmic goiter as we see them now are in brief these: In about two thirds of the cases the inauguration of vigorous roentgen-ray treatment is followed by a progressive improvement, as shown by clinical signs and by the behavior of pulse, metabolism and body weight. This continues for from four to five months, during which time about five suberythema doses of roentgen ray are given to the thyroid and thymus. This improvement may go to the extent of recovery or may fall short of that. When the latter, continuation of the roentgen-ray treatment seems to be of but little value. On the other hand, certain cases that show a marked improvement may later, after the cessation of roentgen-ray treatment, have a return of the hyperthyroidism; in these cases a second course of treatment not infrequently is accompanied by a second rapid improvement.

In other words, the data presented here indicate that the beneficial effect of roentgen ray, if there is to be any such, should be obvious during the first four or five months of treatment. It would seem therefore that the roentgen ray is a useful therapeutic agent in the management of exophthalmic goiter, but it is by no means an ideal one. Patients who do not respond to the roentgen ray in 4 or 5 months, and those who, although improved, still remain somewhat thyrotoxic at the end of that time, should be given the benefit of surgery. Our conception of the proper way of using the roentgen ray in exophthalmic goiter is that in most cases it should be given a trial with the idea that it may effect a cure, or if not, that it may, through reducing the degree of hyperthyroidism, make the patient a better operative risk.

Of course, it may be asked why, if the roentgen ray has no effect in certain cases, should it be used in any case? Why should not all patients be subjected to operation at once? The obvious answer to this is that in spite of the remarkable success of modern operative procedures in the hands of specially skilled surgeons, there still remains

a definite mortality. This mortality, we believe, can be reduced or abolished by not resorting to surgery at once in every case, but by making use of the roentgen ray first, partly because we believe that by such a program some patients may never need operation, while others will be in better shape to stand it at a later date because of their previous irradiation.

Neither roentgen ray nor thyroidectomy is an ideal method of treatment, for neither in all probability attacks the cause of the disease. The cause of exophthalmic goiter is entirely unknown, but it is probable that it does not originate within the thyroid. Nevertheless, the resulting phenomena in the patient, and the ones from which he needs to be protected, are directly due to the overactivity of that gland. Until the cause of the disease is known, therefore, and some agent found which can directly combat that cause, it is reasonable to continue to attack the thyroid. The surgeon seeks to do this by the removal of a portion of the gland. The radiologist tries to destroy some of the tissue in situ. The object is the same; the agent used differs. Neither agent is entirely satisfactory, each may be used to supplement the other.

In the past we have sometimes persisted with the roentgen ray over long periods and given large numbers of treatments, although the patient showed little or no improvement. In view of such experience, we now feel very definitely that this is an undesirable thing to do. The roentgen ray in time seems to lose whatever effect it may have on the thyroid, just as it does ultimately on the leukemic spleen. When it ceases to produce improvement in exophthalmic goiter, it should, in our opinion, be abandoned and thyroidectomy substituted in those cases in which a thyrotoxicosis persists. Every patient with exophthalmic goiter should be made the subject of individual study, and the various therapeutic measures at our disposal should be used alone or combined as that particular case may demand.

In the matter of toxic adenoma, the problem is altogether different. In that disease the cause appears really to lie within the thyroid, in the adenoma in fact.[40] The surgical removal of the tumor cures the disease. There would seem, therefore, not to be the same desirability for preliminary roentgen-ray treatment. We have used the roentgen ray, therefore, in this disease only with patients who have refused operation. Nevertheless, it is interesting to note that they, like those with exophthalmos, show improvement. In fact, all fourteen of our cases so treated improved. In four cases the improvement was slight. In five it was marked, and in five there was a cessation of all signs and symptoms

40. Plummer, H. S.: Interrelationship of Function of the Thyroid Gland and of Its Active Agent Thyroxin in the Tissues of the Body, J. A. M. A. **77**:243 (July 23) 1921.

of thyrotoxicosis. In six cases the goiter disappeared during the treatment. The fact that cases of toxic adenoma improve while under roentgen-ray treatment, as well as cases of exophthalmic goiter, is, we believe, strong evidence that the effect is really the result of the irradiation, for the course of toxic adenoma untreated is continuous. One does not expect spontaneous remission of the sort found in exophthalmic goiter.

It has been our object ever since this research was started to follow our patients for a long period of time. We have been fortunate in being able, in a number of instances, to secure data extending over a period of several years. In dealing with a disease like either of the varieties of toxic goiter, the real benefits of treatment can only be evaluated properly by studying the late results. It was with this ideal in mind that we have introduced in the present paper recent data in cases previously published. The larger series of the last three years which has formed the basis of the above discussion will serve well to illustrate the immediate results of roentgen-ray treatment, but the smaller prewar series will show the results from five to seven years after treatment. Seven out of fifteen patients in that group treated solely by the roentgen ray in whom there was originally apparent recovery, have remained well. Crile has said that the roentgen ray does not control exophthalmic goiter; that it may produce great benefit but with recrudescence, as a rule.[41] This has not been our experience. Recrudescence may occur, but it is not by any means the rule.

Effect of Rest.—In ascribing improvements in any disease to a certain therapeutic agent it is always easy to overlook the factor of rest. This is particularly true of exophthalmic goiter. There is no question that complete rest alone is often accompanied by a decrease in the degree of hyperthyroidism. We have indicated in our charts and tables to what extent rest may have been a factor in the cases under discussion. It seems to us that it is a minor one. Not a few patients showed the characteristic improvement with no rest at all.

Focal Infection.—The matter of focal infection has been given consideration in our clinic. We have made it a practice to remove obvious foci, infected tonsils and the like, but cannot say that we have seen any startling effects from such procedures. Observations before and after tonsillectomy will be found in four of the cases given in Tables 1 and 2 (Cases 338, 591, 603 and 866). We feel that in the management of toxic goiter the correction of infectious foci is impor-

41. Crile, G. W.: Discussion, Symposium on Basal Metabolism in Clinical Medicine, J. A. M. A. **77**:355 (July 30) 1921.

tant, but we have not seen any reason to believe, as McCarrison [42] does, that they are an important factor in the production of the disease. They may serve to aggravate or prolong the thyrotoxicosis.

Pregnancy.—In four cases of exophthalmic goiter we have secured observations before and during pregnancy, and in one case after pregnancy as well. Mrs. A. B. (Case 374) showed a marked improvement with a combination of roentgen-ray therapy and ligation of vessels. She married June 4, 1921; November 16 her metabolism was + 16 per cent.; April 18, 1922, when six months pregnant, it was + 13 per cent. She has had no return of her symptoms of hyperthyroidism. Mrs. J. L. (Case 485) developed myxedema during roentgen-ray treatment. When last seen she was four months pregnant, with no return of symptoms of hyperthyroidism or hypothyroidism. Another woman (Case 762) had failed to respond to the roentgen ray. Later a hemithyroidectomy was done which was followed by some improvement. A definite increase in her thyrotoxicosis manifested itself when she became pregnant, but when three months pregnant a further thyroidectomy was done without interruption of her pregnancy, and when last seen, her metabolism was normal and her symptoms of hyperthyroidism had disappeared. Mrs. F. S. (Case 802) who after recovery following roentgen-ray treatment went through a pregnancy without recurrence, has been referred to earlier.

Cardiac Complications.—Our studies of the cardiac complications have not been as complete as we hope to have them in the future. Ordinary examinations of the heart have been made from time to time, and in the fibrillating cases electrocardiagrams have been taken. We have not, however, carried out any of the newer functional tests of the heart. Our clinical observations have not disclosed any evidence that patients received added cardiac damage because they were treated by the roentgen ray instead of immediate operation. We recognize the need of further study on this problem and propose to make it.

VII. CONCLUSIONS

1. We believe that the data presented here show that the roentgen ray probably has a beneficial effect in toxic goiters, and that for that reason it has its place in our armamentarium for treating these diseases.

2. About two-thirds of the patients with exophthalmic goiter so treated show either recovery or improvement coincident with the treatment. The remaining third neither improve nor grow worse.

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42. McCarrison, R.: The Thyroid Gland in Health and Disease, New York, William Wood & Co., 1918.

3. In exophthalmic goiter, when treated by the roentgen ray, if good results are not secured in a few months, surgery should be employed. Prolonged roentgen-ray treatment in patients showing no response is undesirable. This is a fact which has been impressed on us particularly in our recent work. We have not emphasized it before, and therefore, do so now.

4. Some patients with exophthalmic goiter who are not cured by the roentgen ray are, perhaps, made better operative risks by it. A combination of the two forms of treatment may sometimes accomplish more than either does alone.

5. In toxic adenoma there seems to be a similar improvement to that noted in exophthalmic goiter, but so far we have used it only with patients who have refused operation. In toxic adenoma, in contrast to exophthalmic goiter, surgery probably removes the actual cause of the disease, the adenoma. The indication for surgery would, therefore, seem more definite than in exophthalmic goiter. Even in toxic adenoma, however, in certain cases that are too thyrotoxic for safe operation, the roentgen ray may be used to advantage.

6. To make a proper use of the roentgen ray in the management of toxic goiter of either variety, its limitations should be recognized and it should be intelligently correlated with other therapeutic measures as the individual case may demand.[43]

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43. Since going to press, an interesting article by Drs. Kessel, Lieb and Hyman (J. A. M. A. **79**:1213 [Oct. 7] 1922) has come to our attention. They are supplying data on patients treated by rest alone, which will be of great value in settling some of the disputed matters regarding thyrotoxicosis.

THE CORRELATION OF VITAL CAPACITY WITH STEM HEIGHT *

WILLIAM LESTER ROGERS

SAN FRANCISCO

The vital capacities of normal men vary with their sizes. The measurement of size which furnishes the best standard for estimating the normal vital capacity is, however, still under discussion. In a recent study of male students at Stanford University,[1] a comparison was made between vital capacity, on the one hand, and the height, the weight, and certain combinations of height and weight on the other. The stem heights of these students were not measured; and since Dreyer places the highest value on stem height in estimating the normal vital capacity, the present study was undertaken for the purpose of comparing stem height with standing height as a vital capacity standard for normal young men.

SUMMARY OF PRESENT DATA (STANFORD 2) COMPARED WITH PREVIOUS STANFORD DATA AND WITH A COMBINATION OF STANFORD, HARVARD AND OXFORD DATA

	Stanford (2)	Stanford (1)	Stanford, Harvard and Oxford
Number	400	400	1,444
Means:			
Height	175.9	175.9	176.2
Stem	91.5		
Vital capacity	4,421	4,646	4,426
Standard Deviations:			
Height	6.48	7.121	6.805
Stem	3.30		
Vital capacity	595.7	655.8	646.9
Coefficients of Correlation:			
Height : Vital capacity	0.46	0.55	0.53
Stem : Vital capacity	0.47		
Height : Stem	0.79		

Observations were made on 400 male students at Stanford University, whose ages ranged between 18 and 30 years. The standing heights were measured in bare feet and the stem heights were measured according to the method described and illustrated by Dreyer.[2] Each student was shown how to use the spirometer and was then given three trials, the maximum reading being recorded as his vital capacity.

The accompanying chart shows the average vital capacities for the different stem height groups. Two lines have been added to this figure.

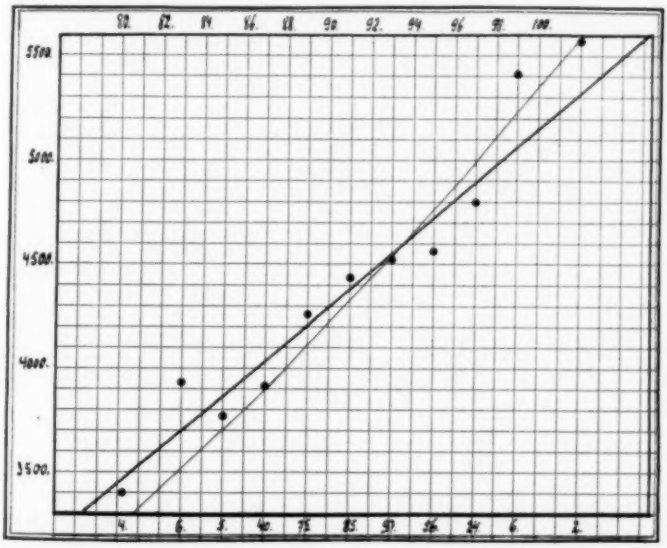
* From the Department of Medicine, Stanford University.

1. Hewlett, A. W., and Jackson, N. R.: The Vital Capacity in a Group of College Students, Arch. Int. Med. **29**:515 (May) 1922.

2. Dreyer, G.: The Assessment of Physical Fitness, New York, Paul B. Hoeber, 1921.

The heavier line represents the linear relation between vital capacity and stem height as calculated from the present data; the lighter line represents the relation given by Dreyer for "Class A" individuals. It will be noted that the slope of Dreyer's line differs somewhat from that which best fits our data, and that, furthermore, for the range of stem heights under consideration, the curve in Dreyer's line is not marked. We see no reason for adopting Dreyer's complex formula, at least for adult men, when a linear formula will answer the same purpose.

The linear relationships between vital capacity on the one hand, and standing height or stem height on the other, can be calculated and



The ordinates represent vital capacities and the abscissas stem heights. The dots represent the average vital capacities for the different stem-height groups, the number of observations in each group being given below. The straight heavier line has been calculated to fit our data. The lighter curved line represents that given by Dreyer for "Class A" individuals.

expressed mathematically by the methods commonly used in statistical studies.[1] The more nearly the coefficient of correlation approaches unity, the closer is the relation between two sets of data obtained from the same group of individuals.

The accompanying table shows the means, the standard deviations and the coefficients of correlation for the present set of observations, together with some corresponding figures taken from the previous paper. It will be observed that the coefficient of correlation between

standing height and vital capacity was 0.46 and that the coefficient of correlation between stem height and vital capacity was 0.47. This difference is not significant.

CONCLUSION

In a group of male college students the correlation between stem height (Dreyer) and vital capacity was not significantly better than the correlation between standing height and vital capacity.

A CLINICAL REPORT ON THE USE OF QUINIDIN SULPHATE*

L. E. VIKO, M.D.; H. M. MARVIN, M.D.,
AND
PAUL D. WHITE, M.D.
BOSTON

INTRODUCTION AND HISTORICAL RÉSUMÉ

Although eight years have passed since Wenckebach [1] noted the restoration of normal rhythm by quinin in cases of auricular fibrillation, there is but little agreement regarding the indications and limitations for the use of this drug or its more effective isomer, quinidin. As Wenckebach found quinin but rarely effective, it was used but little for the four years following his report. Then, in 1918, Frey, testing other alkaloids obtained from cinchona in cases of auricular fibrillation, showed the greater efficacy of quinidin in restoring normal mechanism, and gave the investigation new impetus. This first report,[2] embodying the results obtained in his first twelve cases, was followed by another report on twenty-two cases.[3] Here he outlined the method of administration still used with little change, and noted the advisability of previous digitalization and test dosage with quinidin. His observations on recurrence, toxic and untoward results, and changes in pulse rate have been added to but little since that date. From 1918 to the present date a large number of investigators have reported their observations, usually on small series of cases of auricular fibrillation, which have not permitted very satisfactory conclusions. In 1921, Frey [4] again reported his cases, then fifty in number, confirming his previous observations and commenting on the relation of the duration of the arrhythmia to the results obtained from use of the drug. Boden and Neukirch [5] and others have reported favorable results from use of the drug in paroxysmal tachycardia and premature beats. Later Lewis, Drury, Iliescu and Wedd [6] reported their observations on the mode of action of

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* From the Massachusetts General Hospital, Boston, and the New Haven Hospital, New Haven, Conn.

* Read in part at the annual meeting of the American Society for Clinical Investigation, Washington, D. C., May 1, 1922.

1. Wenckebach, K. F.: Die unregelmässige Herztätigkeit, 1914.
2. Frey, W.: Berl. klin. Wchnschr. **55**:450 (May) 1918.
3. Frey, W.: Berl. klin. Wchnschr. **55**:849, 1918.
4. Frey, W.: Deutsch. Arch. f. klin. Med. **136**:70 (April) 1921.
5. Boden, E., and Neukirch, P.: Deutsch. Arch. f. klin. Med. **136**:181, 1921.
6. Lewis, T.; Drury, A. N.; Iliescu, C. C., and Wedd, A. M.: Brit. M. J. **2**:514 (Oct.) 1921.

quinidin with relation to the circus movement of auricular fibrillation and flutter and so placed the use of the drug upon a rational basis.

During this period of investigation, a number of writers have noted serious untoward results under quinidin: Benjamin and Von Kapff,[7] Ellis and Clarke-Kennedy,[8] Eyster and Fahr,[9] Haass,[10] Sappington,[11] Wilson and Hermann,[12] Hewlett and Sweeney,[13] Frey and others. As these included cases with fatal and nonfatal embolism, increased failure and unexplained sudden death, the profession has questioned the utility of a drug producing such effects. That by its use excellent results obtain in certain cases, many, perhaps most, writers have agreed, and remembering the one hundred years of neglect digitalis suffered [14] following the classical work of Withering in 1785 (and this in an age more open to drug therapy than our own), we hesitate to discard without due trial a drug so potent as quinidin. If it were possible to choose for its use only those cases likely to yield favorable effects and to avoid the cases likely to suffer untoward results, it would seem a valuable therapeutic agent.

During the last year at the Massachusetts General Hospital and the New Haven Hospital a series of cases of the nonparoxysmal ("permanent") type of auricular fibrillation and flutter have been treated with quinidin. This report deals principally with this type of case. In addition a small series of the paroxysmal type of fibrillation and flutter and a few cases showing premature beats or heart block have been observed under the influence of the drug. An attempt has been made to correlate the observations made with those found in the literature. A preliminary report of the present study was published last year.[15]

CASES OF NONPAROXYSMAL AURICULAR FIBRILLATION AND FLUTTER

At the Massachusetts General Hospital and the New Haven Hospital, seventy-one cases of nonparoxysmal ("permanent" or "chronic") auricular fibrillation and four cases of nonparoxysmal flutter have been treated with quinidin sulphate,—a total of seventy-five cases. The first

7. Benjamin and Von Kapff: Deutsch. med. Wchnschr. **47**:10, 1921.
8. Ellis and Clarke-Kennedy: Lancet **2**:894, 1921.
9. Eyster, J. A. E., and Fahr, G. E.: Quinidin in Auricular Fibrillation, Arch. Int. Med. **29**:59 (Jan.) 1922.
10. Haass, H.: Berl. klin. Wchnschr. **58**:540, 1921.
11. Sappington, S. W.: Quinidin Treatment of Auricular Fibrillation, J. A. M. A. **78**:59 (Jan. 7) 1922.
12. Wilson, F. N., and Herrmann, G. R.: Cerebral Embolism Following Arrest of Auricular Fibrillation by Quinidin, J. A. M. A. **78**:865 (March 25) 1922.
13. Hewlett, A. W., and Sweeney, J. P.: Quinidin Treatment of Auricular Fibrillation, J. A. M. A. **77**:1793 (Dec. 3) 1921.
14. Pratt, J. H.: Digitalis Therapy, J. A. M. A. **71**:618 (Aug. 24) 1918.
15. White, Marvin and Burwell: Boston M. & S. J. **185**:647, 1921.

sixty cases were practically unselected; the majority of the remaining fifteen cases were selected on the basis noted below. In nearly all the cases showing congestive failure, digitalis was administered before the use of quinidin was begun. All patients were given 0.2 gm. twice (a two hour interval) the day preceding the full dosage as test doses for sensitivity to the drug. After that the usual method of administration was 0.4 gm. five times daily by mouth in capsule or tablet form at two hour intervals, in some cases increasing to 0.6 or 0.8 gm. five times daily. Usually the drug was continued until restoration of normal rhythm or development of significant toxic symptoms. Each case was

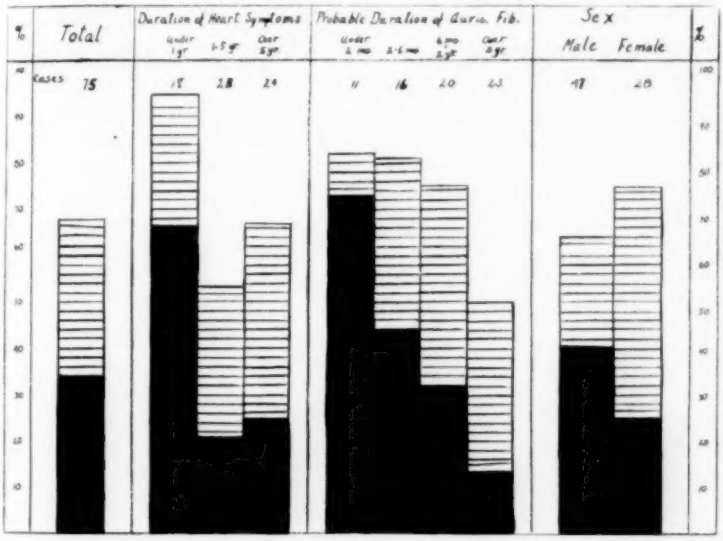

Fig. 1.—*Relation of various factors to restoration and maintenance of normal rhythm.* Abscissas represent the groups of cases under consideration, ordinates the percentage responding to quinidin. The column represents the percentage of a given group restored to normal rhythm, the shaded part those relapsing, the black part those still maintaining normal mechanism. Above each column is noted the number of cases in that group.

studied carefully by the usual laboratory and clinical methods and by electrocardiograms at least once daily. Seven of the patients were handled as outpatients, all the others remaining in the hospital during the period of quinidin administration.

Total Series.—Of the total series of seventy-five cases, fifty-one cases, or 68 per cent., were restored to normal rhythm by quinidin; twenty-six cases, or 34 per cent., still maintain it after intervals varying from a few days in the last case to more than ten months (Case 6).

In other words, in a largely unselected series of cases two-thirds were restored to normal rhythm and one-third maintain it (Fig. 1).

Sex.—Though a higher percentage of females than males were restored to normal rhythm, a lower percentage maintained it (Fig. 1). Sex cannot be considered an important factor in determining restoration or relapse.

Age.—Consideration of the age of the patient (in groups of ten year periods) with relation to the restoration and maintenance of normal mechanism showed that while patients more than 50 years of age presented a higher percentage of restoration than those between 30 and 50, the percentage of maintenance was strikingly equal. The low percentage in the first group (ages from 20 to 29) may have been the result of the small number of cases in that group. There was, then, no marked parallelism between age and response to quinidin (Fig. 2).

Etiologic Type of Heart Disease.—Four cases of the series were of doubtful etiology. The remaining seventy-one cases were divisible into four groups: rheumatic, arteriosclerotic, thyroid, and thyroid plus rheumatic. The last two groups, containing only three cases each, were too small to permit drawing conclusions as to their relative response to quinidin. The arteriosclerotics had a higher percentage of restoration (76 per cent.) than the rheumatics (61 per cent.), and a higher percentage of maintenance (43 per cent. as compared to 27 per cent. for the rheumatic) (Fig. 2). Since the arteriosclerotic group comprises largely the older patients, these observations correspond roughly to the variations with age as noted above. That this difference in response may be due to a factor other than the etiologic type will be considered later in this communication under the discussion of the variation in response with respect to congestive failure.

Duration of Heart Signs or Symptoms.—The actual duration of the cardiac disease being difficult to estimate, the duration of heart symptoms or recognized signs was considered for its possible relation to response to quinidin (Fig. 1), dividing the cases into three groups and excluding five cases in which the duration was questionable.

The cases in the group of from one to five years' duration had a reasonably equal percentage of maintenance of normal rhythm (21 per cent.) with the cases of more than five years' duration (25 per cent.); the latter of the two groups had a slightly higher percentage of restoration (66 per cent. as compared with 53 per cent. for the group of cases of shorter duration). The group of eighteen patients whose cardiac symptoms were of less than one year's duration had high percentages of restoration (94 per cent.) and maintenance (66 per cent.). These differences will be referred to again in the discussion of the relation of duration of fibrillation to response to quinidin.

Probable Duration of Fibrillation.—In all of the cases, except five, it was considered possible, by careful history taking, use of outpatient records or reports from the patient's previous physician to approximate the probable duration of fibrillation or flutter. Grouping the remaining seventy cases according to this duration, a striking parallelism appeared both to restoration and maintenance of normal rhythm (Fig. 1). Of the group of eleven cases with fibrillation of less than two months' duration, 82 per cent. were restored to sinus rhythm and 73 per cent. maintain it. Of the cases, twenty-three in number, with a fibrillation more than two years old only 48 per cent. were restored and but 13 per cent. maintained normal mechanism. Duration of fibrillation seems to be the most important factor determining response to quinidin.

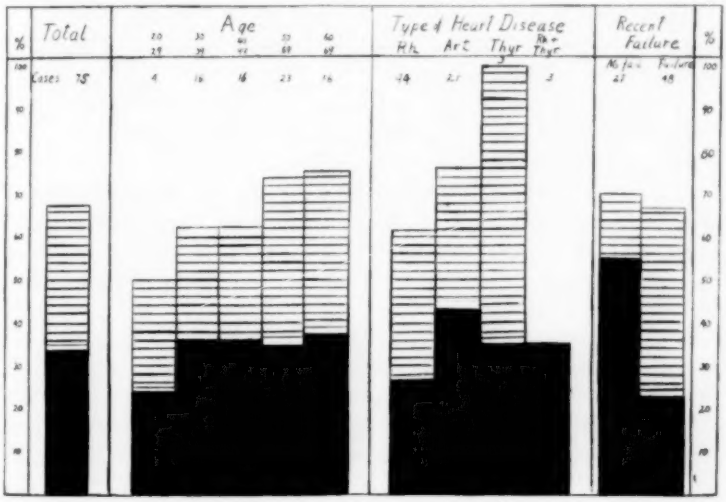

Fig. 2.—Similar to Figure 1.

In discussing the variation in response with relation to duration of heart symptoms (Fig. 1) a higher percentage of favorable results was noted in the first group; of the eighteen cases in this group only three had fibrillation of more than six months' duration, and it is probable that the latter factor was the one responsible for the response in that group. Similarly, the slightly better results in the third group than the second group may be explained by the fact that of the second group only 19 per cent. had fibrillation of less than six months' duration, while 27 per cent. of the third group had fibrillation of such short duration.

Failure of the Congestive Type.—While those cases showing objective congestive failure (edema, enlarged liver, pulmonary edema, etc.)

on admission were restored to normal mechanism in about an equal percentage to those not showing such failure, the percentage of maintenance in the former was less than half that in the latter (Fig. 2). A similar tabulation of cases showing such failure at the beginning of quinidin administration (after digitalization) yielded similar results. Though cases with failure may be restored as readily as the others they present a much greater tendency to relapse.

In the consideration of the relative response of the rheumatic and arteriosclerotic types, it was noted that the latter responded more frequently than the former; this difference may have been due, in part at least, to the greater frequency of congestive failure in the cases of the rheumatic group (72 per cent.) than in the arteriosclerotic group (57 per cent.).

Cases with a history of periods of failure in the past seemed to respond poorly to quinidin whether or not there was marked failure at the time of quinidin treatment.

It was of interest to note that congestive failure was about equally frequent in the groups of patients with auricular fibrillation of short duration and in those of long duration.

Congestive failure (objective), the expression of myocardial failure appears to be the second of the two important factors determining response to quinidin. Presumably, the weakened cardiac muscle is in some way more resistant to the influence of quinidin than the normal or less damaged muscle.

Digitalization with Relation to Response to Quinidin.—As only five patients of the series had not received digitalis prior to quinidin, it was not possible to determine comparative response between digitalized and nondigitalized cases. However, the fact that congestive failure was unfavorable for the production of maintained normal mechanism suggested that, in cases with such failure, digitalis probably favored rather than antagonized the action of quinidin. In a large number of cases heavy digitalis dosage was given just prior to quinidin and yet normal rhythm appeared, often with the smallest doses of quinidin. All the cases, except two, in which restoration of normal rhythm was not obtained or was transient, apparently reacted quite as well to digitalis as before the use of quinidin. The two exceptions, in which a "fixed flutter" was produced by quinidin will be described later. From these observations it appeared not only that there was little or no antagonism between the two drugs but also that digitalis was distinctly indicated in cases with failure before the initiation of quinidin.

Quinidin Dosage.—In the cases restored to normal rhythm, the total dosage varied from 0.4 gm. (the test doses only) in two cases to 23.2 gm., the period of administration from one-half day to ten and one-half

days, the daily dose from 1.6 gm. to 4 gm. and the single dose from 0.2 gm. to 0.8 gm. Of the fifty-one cases restored, 86 per cent. required less than 9 gm. total dosage. There was no close correspondence between the duration of fibrillation and the dosage required to restore normal rhythm (Fig. 3). There was essentially no greater tendency to relapse in the cases requiring large dosage than in the cases in which small doses were sufficient. Some of the cases requiring the largest dosage have given the most satisfactory clinical results. In the reported cases of untoward results under quinidin, the dosage has usually been small. While the present lack of exact knowledge of the drug inclines one to keep the total dosage within the limits under which

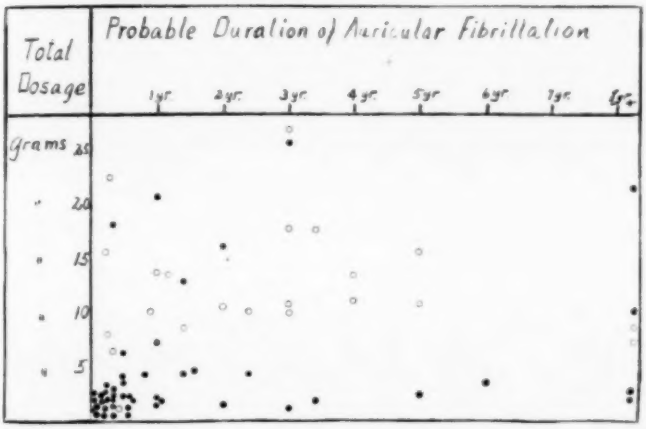

Fig. 3.—*Relation of dosage to probable duration of fibrillation.* The black dots represent those cases restored to normal rhythm, the circles those cases not restored. Abscissas = duration of fibrillation; ordinates = dosage of quinidin given.

the majority of patients react, observations to date have presented no contraindications to the use of the large doses, and it may be that in a favorable case under close observation the drug should be continued until normal rhythm is established or toxic symptoms develop.

Thirteen patients either failing to respond to the first course or relapsing immediately were given subsequent courses. Only two of those restored by such additional courses still maintain normal mechanism. When a patient fails to respond to an adequate first course or relapses quickly, further quinidin is usually not worth while.

After restoration of normal rhythm, twenty-four of the fifty-one patients (usually alternate cases) were given rations of quinidin in varying doses over varying periods. About an equal percentage

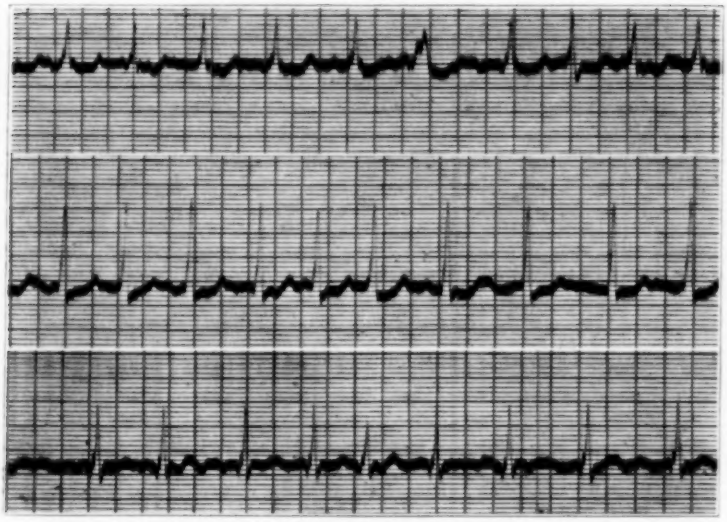

Fig. 4.—Electrocardiogram of R. M. Auricular fibrillation (before quinidin), Leads I, II and III.

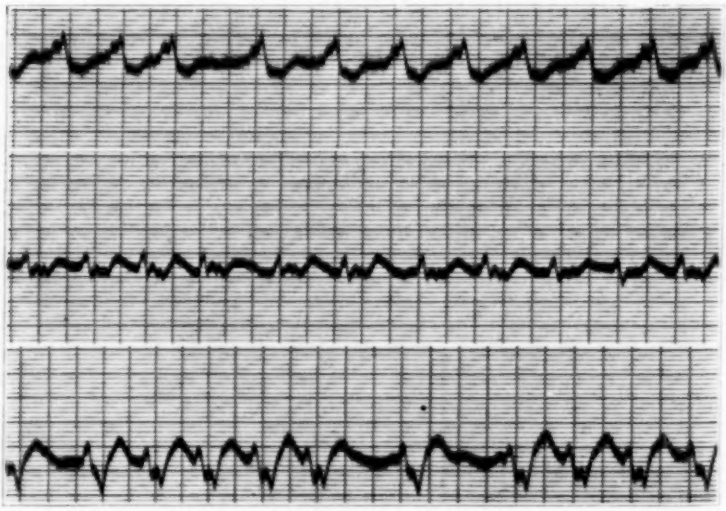

Fig. 5.—Auricular fibrillation. Bundle branch block.

relapsed in those rationed and those not rationed. As the cases rationed were generally more favorable for relapse (a higher percentage of cases with fibrillation of long duration) than those not so treated, the rationing did not prove so ineffective as the figures suggest. In addition, the dosage given in the earlier cases later proved to have been entirely inadequate. Patients with fibrillation of short duration and no failure need less rationing after reestablishment of sinus rhythm and possibly in some cases none at all. One patient reported four months after restoration with paroxysms of fibrillation that have been entirely prevented to date by rations of 0.4 gm. daily. At New Haven, Marvin gave routine rations of 0.4 gm. three times daily the first two days after restoration, twice daily the succeeding two days, once daily the next two days and then once weekly and considered this method to be usually effective. At the Massachusetts General Hospital as high as 0.4 gm. daily over periods of from several weeks to months have been given in some cases with no apparent ill effects. Only further study will determine whether such long continued dosage bears hidden ill effects.

Changes in Cardiac Mechanism.—A number of interesting changes in the cardiac mechanism appeared during quinidin administration. Even without direct chest leads, many cases demonstrated definite slowing of the auricular circus rate before or without restoration of sinus rhythm. Auricular flutter was observed in seventeen cases; of these, eleven later attained normal rhythm, two remained "fixed" in flutter despite digitalis and additional quinidin and four reverted to fibrillation. Under quinidin transient bundle branch block occurred in two cases, one during the transition to normal rhythm, the other without restoration of sinus mechanism (Figs. 4 and 5). The first of these cases presented at the same time a regular tachycardia without evident *P* waves. Four other cases showed transient intraventricular block of lesser degree (aberration type) (Fig. 6), all but one during the period of transition to normal rhythm. One other case for some hours before the appearance of normal rhythm showed a regular slow rhythm with no evident *P* waves.

In fourteen cases the *P R* interval after restoration of sinus rhythm exceeded 0.18 seconds. As all of these patients but one had been previously digitalized (and usually had an inverted or diphasic *T* wave), digitalis was considered at least partially responsible for the *A V* block. In the case not previously digitalized, the *P R* interval remains long five months later, though no digitalis or quinidin has been given in the interval; here the block is probably organic rather than the result of quinidin administration. One other case still main-

tains a long *P R* interval months after cessation of digitalis and quinidin. Of the others, three, later, became normal in length, one is still under observation and in the other eight fibrillation recurred before the persistence of the *A V* block could be estimated.

In ten cases ectopic beats persisted after restoration of normal mechanism; such cases tended to relapse to fibrillation early, only one still maintaining sinus rhythm.

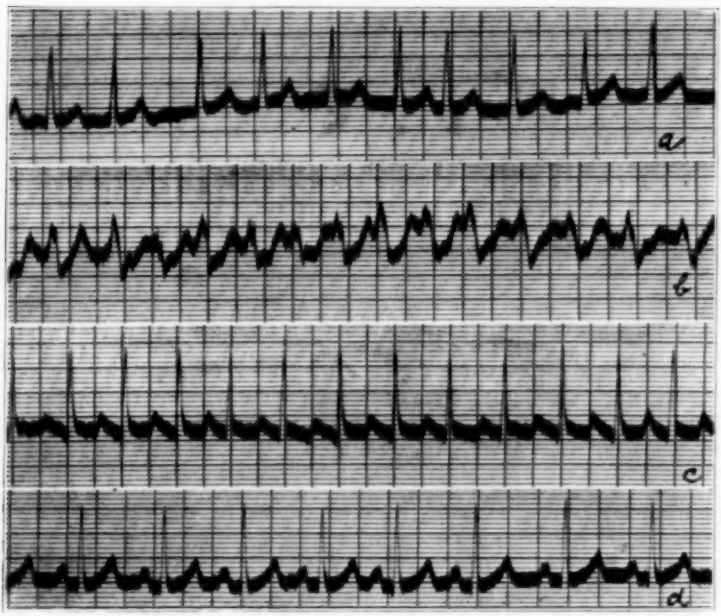

Fig. 6.—Electrocardiogram of N. P. *a.* Auricular fibrillation (before quinidin). Lead II. *b.* Auricular fibrillation. Intraventricular block. Lead II. *c.* Auricular flutter. Lead II. *d.* Normal rhythm. Lead II.

Cases with "fine" and "coarse" fibrillation gave equal percentages of restoration (68 per cent.) in the sixty-three cases in which the type was noted.

Untoward Results.—Transient, unimportant toxic symptoms, disappearing on cessation of the drug appeared in many cases; the most common, in order of frequency, were headache, tinnitus, nausea, vertigo, disturbed vision, vomiting, palpitation and diarrhea. General malaise, precordial pain, nervousness and drowsiness occurred in one or two cases, possibly as effects of quinidin.

In five cases, or 6.6 per cent., more or less serious untoward results occurred (Table 1). In one case quinidin produced a "fixed flutter," in which digitalis later induced a four to one block; while the resulting regular slow ventricular rate should theoretically have been as satisfactory as a slow ventricular rate in fibrillation the patient showed increased cardiac symptoms for some time. In one case quinidin produced a "fixed flutter" which persisted as flutter with a ventricular rate of from 140 to 160, with increasing failure until death fourteen days after its onset. Necropsy showed in addition to marked congestive failure pulmonary embolism, presumably from auricular thrombi as foci. It is probable that the production of such "fixed flutter" can be avoided by the cessation of quinidin within twenty-four hours after the onset of the flutter. In one case a transient peripheral unimportant embolism followed the restoration of normal rhythm; the circulation was unaffected and this patient was much benefited by the treatment. One patient died suddenly a few hours after normal rhythm appeared; no

TABLE 1.—UNTOWARD RESULTS

	Number of Cases
Fixed flutter—4 to 1 block; patient little harmed	1
Fixed flutter—Pulmonary embolism; death	1
Embolism—Peroneal artery; unimportant	1
Sudden death—? embolism; no necropsy	2
	5 (6.6%)

necropsy was permitted. In the fifth case, the patient had been restored to normal rhythm for several days and then relapsed to fibrillation. Digitalis was begun and three days later she died quite suddenly. No necropsy permission was obtainable.

The scarcity of necropsies in such cases of sudden death under quinidin is unfortunate. The most likely cause of death is massive pulmonary or cerebral embolism. If ventricular fibrillation were responsible, as has been suggested, one would have expected the second of our two patients to have died at the time quinidin was at its maximal concentration and not three or four days later. In cases in which normal rhythm is produced, the lengthening of the refractory period that breaks up the auricular circus is predominant;[6] it does not seem likely that in such a case the drug induces ventricular fibrillation. The answer must come from necropsies and from electrocardiograms at the moment of onset—if more such unfortunate cases occur.

All five of the cases in which serious untoward results occurred had congestive failure and, on admission, a history of one or more periods of such failure in the past was given. Three of the patients had fibrillation of more than a year in duration. That this is the type of case likely to develop untoward results will be noted later.

Benefit from Restoration of Normal Rhythm.—In some of the cases the benefit from the restoration of normal rhythm was so striking that it was unquestionable. In others, the persistence of the effect of previous digitalization had to be taken into consideration in estimating the part played by quinidin. In cases without objective failure, the temperament of the patient had to be considered in evaluating the subjective improvement noted. Vital capacity readings were of value and usually corresponded to the other clinical evidence of improvement. In noting benefit from quinidin (Table 2) all these factors have been taken into consideration.

GROUP 1 (Table 2).—Two of the five cases not digitalized before quinidin showed what was considered definite improvement from restoration of normal rhythm.

GROUP 2.—Four cases failing to respond to adequate doses of digitalis and presenting tachycardia, objective congestive failure, or both

TABLE 2.—BENEFIT FROM QUINIDIN

Group	Previous Digitalization	Response to Digitalis	Normal Rhythm by Quinidin	Relapse	Benefit from Quinidin	Number of Cases
1	None	.....	Yes	No	Moderate to marked	2
2	Yes	Poor or none	Yes	No	Moderate to marked	4
3	Yes	Good	Yes	No	Moderate to marked	15
						21(28%)
4	Yes	Good	Yes	No	Slight or none	7
5	Yes	Usually good	Yes	Yes	Slight or none	23
6	Yes	Usually good	No	...	None	24
						54(72%)

when quinidin was begun, showed marked improvement from restoration of sinus rhythm with slowing of the heart and disappearance of the congestive failure. In two of these the effect was striking.

GROUP 3.—Fifteen cases responding moderately or well to digitalis presented definite additional improvement after the reestablishment of normal rhythm. In cases with objective failure persisting after digitalization, this diminished or disappeared. One case is particularly worthy of mention: A physician, whose ventricular rate had been well controlled by digitalis for months, had, nevertheless, been forced to give up his practice because of dyspnea and palpitation on slight exertion. Following the restoration of normal rhythm, he resumed his practice and has continued active work since that time. As he had no objective failure, it is possible that part of the limitation of activity he suffered prior to quinidin was the result of his mental reaction to a knowledge of heart disease; in this case it seems unlikely, but even so the fact remains that through quinidin a valuable man has returned

to activity in his community. This is one of the types of cases most favorable for the use of quinidin.

Twenty-one patients, or 28 per cent., received from moderate to marked clinical improvement from quinidin. It is to be noted that of these, sixteen had fibrillation of less than one year's duration and the majority of less than six months'; also that in all but four of these cases the benefit was additional to that obtained from digitalis. It may reasonably be assumed that if 28 per cent. of the cases are benefited in a largely unselected series, a considerably larger percentage would be obtainable in a group of selected cases.

Advantages of Normal Rhythm.—The relative utility of quinidin or quinidin after digitalization and digitalis alone in cases of auricular fibrillation depends on the relative efficiency of the heart when auricles and ventricles beat regularly in sequence and when there is no auricular systole but a slow ventricular rate (as in the digitalized fibrillating heart).

From the clinical point of view the cases of Group 3 (Fig. 6) suggest the greater efficiency of the heart in normal rhythm. Recently, Stewart and Carter [16] have reported some interesting observations on blood gases before and after restoration of normal rhythm. Their findings point to a greater efficiency of the cardiorespiratory mechanism under normal rhythm than with a fibrillation, even if the ventricular rate is slow in the latter case.

From an experimental point of view, estimation of cardiac efficiency is difficult and none too accurate. Working with animals several investigators compared cardiac efficiency in fibrillation and normal rhythm, taking cardiac output or blood pressure changes as the criterion of cardiac efficiency. In most cases, however, they dealt only with fibrillation in which the ventricular rate was rapid, a condition not quite comparable with the slow heart of digitalized auricular fibrillation in man. For this reason Lewis' conclusions [17] that the decreased efficiency in fibrillation was simply a factor of increased ventricular rate are not entirely applicable to the present problem. Gesell [18] produced a slow ventricle by blocking *A V* conduction in his fibrillation experiments and concluded that the lowered efficiency of the fibrillating heart resulted from the absence of auricular contractions. Lewis stated that faults in Gesell's technic vitiated the value of his conclusions. More

16. Stewart, H. J., and Carter, E. P.: Blood Gases in Auricular Fibrillation and After Restoration of the Normal Mechanism, J. A. M. A. **78**:1751 (June 3) 1922.

17. Lewis, T.: J. Exper. M. **16**:395, 1912.

18. Gesell, R. A.: Am. J. Physiol. **29**:32, 1911.

recently Eyster and Swarthout,[19] in experiments similar to those of Lewis, concluded that auricular fibrillation and flutter "produced a variable reduction in the volume output of blood from the ventricles . . . the effect greater in fibrillation than in flutter and mainly due to the irregularity of the ventricles and to the high percentage of premature and abortive beats, rather than to the fast ventricular rate."

Many patients who have fibrillation live for years; a large percentage of cardiac patients dying have fibrillation. Can we prolong the lives of these patients by restoration of normal rhythm? Years of observation may or may not give us the answer. Many patients with auricular fibrillation live in great discomfort and with markedly restricted activity despite digitalis. That in many such cases restoration of normal rhythm promotes comfort and increases the ability of the patient to carry on a more normal life seems quite certain. In favorable cases in which relapse is less likely, the quinidin cases seem to need no more, perhaps less supervision than digitalis cases. By the restoration of normal rhythm with quinidin we have not removed the underlying heart disease on which the fibrillation is based, but often the precipitating cause for the fibrillation—thyrotoxicosis, acute infection, overexertion, emotional strain, etc.—is long since past. Perhaps, after regaining sinus rhythm, we may be able to guard the patient against further precipitating cause.

Other Observations.—In the thirteen cases in which teleroentgenograms were taken before and after restoration of normal rhythm, no constant change in the shape of the heart was made out and measurements including the Von Zwaluwenburg auriculoventricular ratio[20] showed no significant changes.[21]

The white blood count in forty-three cases followed showed no significant changes during quinidin administration.

UNTOWARD RESULTS WITH AND WITHOUT QUINIDIN

A number of serious untoward results have been reported under the use of quinidin in auricular fibrillation. Of these, embolism and sudden death have been most frequent. That embolism occurs in fibrillation under ordinary treatment not including quinidin is well known, but its frequency is possibly not generally realized. It was, therefore, of interest to compare the frequency of embolism and other

19. Eyster, J. A. E., and Swarthout, E. C.: Experimental Determination of Influence of Abnormal Cardiac Rhythms on Mechanical Efficiency of Heart, Arch. Int. Med. **25**:317 (March) 1920.

20. Van Zwaluwenburg, J. G.: Am. T. Roentgen **7**:1, 1920.

21. We are indebted to the roentgen-ray department at the Massachusetts General Hospital and to Dr. D. S. Dan in particular for cooperation in the roentgen-ray work.

untoward results under quinidin in 484 cases of fibrillation reported (including the present series) with the frequency of embolism in 200 consecutive cases of auricular fibrillation at the Massachusetts General Hospital not receiving quinidin. Each series includes some cases in which no necropsy was obtained to confirm the diagnosis, but as far as possible the same criteria were used in each group (Tables 3 and 4).

Of the nine patients (4.5 per cent.) of the nonquinidin group that suffered embolism while in the hospital, one suffered sudden death (clinically similar to the sudden death under quinidin), although having

TABLE 3.—UNTOWARD RESULTS IN CASES TREATED WITH QUINIDIN

484 Cases (+)	Number of Cases		
Fixed flutter with embolism (present series)	1		
Embolism: Died 3 patients, recovered 2 patients (present series, Ellis and Clarke-Kennedy,[8] Johns Hopkins,[22] Wilson and Hermann [12]	5		
Sudden death (present series, Benjamin and Von Kapff,[7] Sappington,[11] Hewlett and Sweeney,[13] Johns Hopkins [22])	6	15 3.1%	
Possible embolism as cause of death (Bergmann,[20] Benjamin and Von Kapff [7])	3		
Respiratory paralysis (Frey [4])	2		22 4.5%
Miscellaneous: Collapse, increased failure (Frey,[4] Eyster and Fahr,[9] Haass,[10] Hewlett and Sweeney [13])	4		
Fixed flutter (present series)	1		

TABLE 4.—EMBOLISM IN CASES NOT TREATED WITH QUINIDIN—200 CASES

	Number of Cases	
Embolism while in the hospital	9 (4.5%)	
Entered hospital following embolism	7 (3.5%)	8.0%
Recovered from embolism	6	
Died: Sudden death, probably embolic	1	
Embolism immediate cause	5	
Embolism only partly cause	4	

comparatively good circulation. No necropsy was obtainable in this case to confirm the clinical diagnosis of pulmonary or cerebral embolism. Besides these nine cases an additional seven cases, or 3.5 per cent., entered the hospital following embolism. In comparison with the quinidin cases these last cases should not be included.

In the 484 quinidin cases reported in the literature, the total serious untoward results totaled twenty-two cases, or 4.5 per cent.; this included nine cases of embolism and six cases of sudden death probably due to embolism. If the latter are included as cases of embolism there were fifteen cases of embolism, or 3.1 per cent. Including the cases reported by Sappington,[11] by Wilson,[12] and the two Johns Hopkins cases,[22] the total number of cases treated by these investigators was not known so that the percentage of untoward results given is actually a little high in this respect.

22. Personal conversation with Dr. C. S. Burwell.

Such comparison of untoward results in cases with and without quinidin is not intended to suggest that quinidin is not responsible for such effects. The chronologic relationship between restoration of normal rhythm and embolism or sudden death forces the conclusion that the changed mechanism is responsible. Probably the newly arisen contraction of the auricles forcing out auricular thrombi into the circulation produces the emboli and thus also the sudden deaths. That the percentage of untoward results under quinidin as given here is too low is quite possible, as some cases may not have been reported or included here. On the other hand, two of the cases that are included should, perhaps, have been omitted; the case of Haass [10] (collapse under quinidin) because the drug was given intravenously, and one of Benjamin and Von Kapff [7] which I myself considered not the result of quinidin. So it seems justifiable to conclude that embolism is at least not much more frequent under quinidin treatment than under ordinary therapy. Sudden death, however, is considerably more frequent (1.2 per cent. in quinidin cases as compared with 0.5 per cent. in the others).

Study of the twenty-two cases in which untoward results occurred under quinidin, in hope of determining the type of case likely to develop such effects, was rendered difficult by incompleteness of data available in some cases. However, two factors were outstanding and suggestive. A high percentage of the cases presented auricular fibrillation of long standing and an even higher percentage showed objective congestive failure at the time of treatment, in the past, or both. It seems reasonable to suppose that both these factors favor auricular thrombosis and may thus be indirectly responsible for embolism.

OBSERVATIONS OF PREVIOUS INVESTIGATORS IN CASES OF AURICULAR FIBRILLATION

Most of the observations made in this series of cases of fibrillation treated with quinidin agree with those of previous investigators. The importance of the duration of fibrillation and presence of congestive failure in determining the response to quinidin has been noted by most of the investigators who studied large series of cases. Frey [4] Oppenheimer and Mann,[23] and Hewlett and Sweeney [13] referred particularly to the first factor and Frey, Benjamin and Von Kapff,[7] and Hamburger [24] to the latter. Bock,[25] reporting thirty-five cases, laid emphasis on the value of rationing in insuring the maintenance of normal rhythm.

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23. Oppenheimer, B. S., and Mann, Hubert: Clinical Experience with Quinidin in Auricular Fibrillation, J. A. M. A. **77**:1800 (Dec. 3) 1921.

24. Hamburger, W. W.: Effects of Administration of Quinidin Sulphate in Auricular Fibrillation, J. A. M. A. **77**:1797 (Dec. 3) 1921.

25. Bock, G.: Med. Klin. **17**:1052, 1921.

Frey, in particular, concluded that there was great relief to the patient with restoration of normal mechanism. Nearly all investigators favor previous digitalization in cases with failure and apparently consider that this does not hinder the action of quinidin. The observation of Bock that the drug is particularly indicated in hypertonia and peripheral arteriosclerosis was not confirmed by the observations of this series. The observation of one writer that valve lesions were unfavorable to restoration was not confirmed.

QUINIDIN IN PAROXYSMAL FIBRILLATION AND FLUTTER

At the Massachusetts General Hospital eight cases of paroxysmal auricular fibrillation and one case of paroxysmal auricular flutter have been treated with quinidin. Because of the variability in frequency and length of paroxysms without treatment, conclusions should only be drawn in this type of case after long periods of observation. Hence, a detailed report of these cases will not be made at this time.

After some experimentation with dosage 0.4 gm. of quinidin sulphate daily seemed the average effective dose. If an attack occurred in spite of this dosage two or three similar additional doses at two hour intervals were given at the onset of the attack. This daily dose continued for a period of months in several cases and failed to produce any observable ill effects, except transient deafness in one case.

In the one case of paroxysmal flutter treated, quinidin was ineffective and was discontinued. In two of the cases of paroxysmal fibrillation the attacks have almost completely ceased since the administration of quinidin. These patients are most enthusiastic.

Four other patients under shorter periods of observation seem much improved. In the other two cases, the data are at present incomplete. The observations to date give the impression that quinidin will prove of much value in the treatment of paroxysmal auricular fibrillation.

Notes on Cases of Premature Beats.—Only three cases of premature beats (in absence of fibrillation) have been given quinidin; in one no benefit was obtained; in a second the abolition of the premature beats seemed to be associated with a rise in ventricular rate and reappeared as the rate decreased; in the third case quinidin seemed of definite value. It is to be noted that in ten of the cases of "permanent" auricular fibrillation, ectopic beats persisted after the restoration of normal rhythm and this despite the considerable dosage of quinidin that had been given.

Notes on Cases of Heart Block.—Quinidin given in one case of complete *A V* heart block produced no observable effect, toxic or therapeutic. In one case of partial *A V* block quinidin dropped beats became more frequent, and symptoms of the Stokes-Adams type more

marked. Two cases of the fibrillation series and one of the premature beat cases showed bundle branch block before the administration of quinidin; this showed no change under the drug. Quinidin produced transient bundle branch block in two cases and intraventricular block of the aberration type in four cases of the fibrillation series.

The drug seems to be of no value in heart block and may, on the contrary, be distinctly harmful.

SUMMARY AND CONCLUSIONS

A. *Nonparoxysmal ("Chronic," "Permanent") Auricular Fibrillation and Flutter.*—1. Of the seventy-five largely unselected cases of nonparoxysmal auricular fibrillation or auricular flutter in this series, approximately two-thirds were restored to normal rhythm by quinidin and approximately one-third (twenty-six cases) still maintain normal rhythm.

2. Sex is not an important factor in determining restoration or maintenance of normal rhythm.

3. Patients of different ages respond about equally well to quinidin.

4. Other factors being equal the rheumatic and arteriosclerotic types of heart disease respond to the drug equally well. The presence or absence of valvular disease in itself is not an important factor in determining response to quinidin. Too few cases of thyroid etiology have been treated to determine the relative response of these cases.

5. The duration of the heart symptoms is of importance as a factor in determining response only so far as it is associated with two other factors: the duration of auricular fibrillation and the degree of congestive failure.

6. The most important factor in determining both restoration of normal rhythm and its maintenance is the duration of the auricular fibrillation. Cases with fibrillation of short duration (under six months) are not only more likely to be restored to normal mechanism but are much more likely to maintain it even without rations, and, as a rule, give the best clinical results.

7. The second most important factor in determining response to quinidin is the presence or absence, past or present, of objective congestive failure. Cases with objective failure are restored to normal rhythm about as frequently as those without such failure; the former, however, relapse very much more frequently.

8. All cases showing objective congestive failure or tachycardia should probably be digitalized before beginning quinidin treatment. So far as was observed such digitalization does not hinder the response to quinidin, and by reducing the degree of failure favors response and may prevent untoward results.

9. Though most cases responding to quinidin do so with small dosage, many of the most satisfactory cases require large dosage. This is apparently independent of the duration of fibrillation.

10. Proper rationing with quinidin after restoration of normal rhythm will probably reduce the number of relapses.

11. Embolism and sudden death (possibly also due to embolism) occurring under quinidin therapy are probably most likely to occur in cases with fibrillation of long duration and those where there is objective congestive failure at the time or in the past. Hence, the cases most likely to yield serious untoward results are the cases least likely to obtain a maintained normal rhythm from quinidin.

12. A fair percentage of cases, particularly those with recent fibrillation and little or no objective congestive failure, receive definite benefit from restoration of normal rhythm-benefit apparently additional to that obtainable from digitalis alone. The clinical results appear to justify the use of the drug in cases with fibrillation of short duration and with little or no congestive failure. In this type of case untoward results are probably no more common than under the other methods of treatment. For the present quinidin should probably not be used in a routine way in other types of cases. For the present, at least, quinidin should be used in hospitals where careful observation and electrocardiographic control is possible.

B. *Paroxysmal Auricular Fibrillation.*—Quinidin will probably prove of much value in the prevention and treatment of paroxysmal auricular fibrillation.

C. *Premature Beats and Heart Block.*—The data at present available are inconclusive regarding the value of quinidin in treating cases with premature beats.

Quinidin is not indicated for the treatment of heart block.

ENLARGEMENT OF HEMAL NODES*

MAX LEDERER, M.D.

BROOKLYN, N. Y.

Extraordinary enlargements of the hemolymph or hemal nodes are extremely rare. These structures, normally present in the human body, almost always of minute size, are usually overlooked in the postmortem examination. Comparatively few references are found in the literature calling attention to these most interesting tissues. They were first described by Lydig in mammals, i. e., in the hog and sheep, in 1857, and by H. Gibbs in the human being in 1884. The results of systematic examination for these bodies in the human being were first described by Warthin[1] in 1901, and Meyer[2] made an elaborate study of these bodies in the sheep in 1908. In the article by Warthin passing mention of hemolymph nodes is made by pathologists of note who regarded them as of no great significance.

The discoverers of these structures named them hemolymph nodes because of their appearance and microscopic structure. Warthin, however, apparently considers the blood vascular elements, both anatomically and functionally, as the predominant characteristics and suggests as a fitter designation "hemal nodes."

These nodes in the normal state exist as small bodies, very tiny in size, deeply imbedded in the prevertebral fat, lying near a large blood vessel, usually a vein. They are situated, as a rule, near the renal vessels, or in the prevertebral fat of the abdomen or mediastinum. In order to demonstrate them, Warthin recommends dissecting out the prevertebral fat en masse and holding it to the light, when the structures become visible as small red streaks or spots of blood. Occasionally they occur as small nodules of soft consistency.

Because of their gross and so-called microscopic resemblance to splenic tissue, they have been regarded by some as spleniculae and, indeed, at least macroscopically, they may resemble accessory splenic bodies very closely. However, their consistency is very much softer and they are much more collapsible than is splenic tissue. In fact, so impressive to some observers is this resemblance, that a splenic relationship, morphologically and physiologically has been ascribed to them.

For a detailed anatomic and histologic description reference should be made to Warthin's work. Briefly, they vary in size from that of a

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* From the Pathological Department of the Jewish Hospital.

1. Warthin: Am. J. Anat. **1**:63, 1901.
2. Meyer: Anat. Rec. **2**:62, 1908.

pinhead to a large cherry or almond. Occasionally, because of ruptures they may be surrounded by blood or be imbedded in a blood clot and escape observation for that reason. They are surrounded by fat and are always described as lying in the posterior part of the thoracic or abdominal cavities. They look like congested lymph nodes or accessory splenic bodies. Their shape may be that of the spleen. They are bluish gray or slate in color. On section, the resemblance to splenic tissue is quite marked. The pulp is homogeneous, streaked here and there with trabeculae and spotted with dew drop-like malpighian bodies. The parenchyma is surrounded by a well defined capsule.

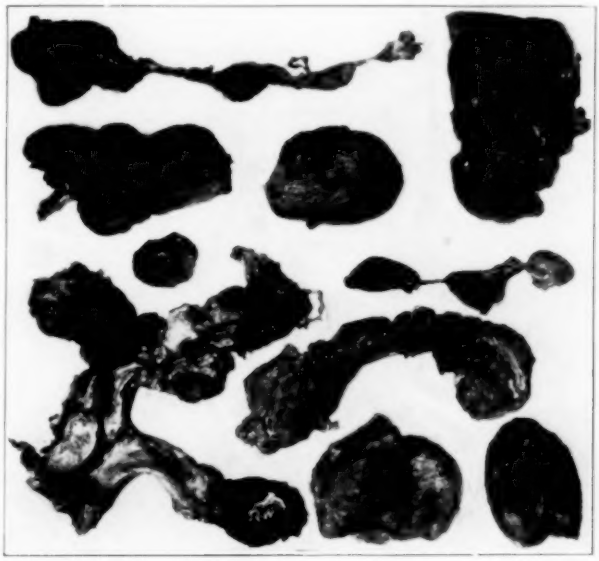

Fig. 1.—Hemal nodes; natural size.

Microscopically, the tissue is seen to consist of numerous blood sinuses lying in a mixture of connective tissue stroma and a variable amount of lymphoid tissue arranged diffusely or in follicles. According to Warthin, the sinuses are traversed by connective tissue fibrils breaking them up into compartments, and in the latter lie red and white blood cells.

Under normal conditions these structures are not numerous and if they are increased in number, many do not attain great size. Symmers [3] describes two cases of tumors of the hemal nodes. In the one case,

3. Symmers, Douglas: Primary Hemangiolymphoma of Hemal Nodes: An Unusual Variety of Malignant Tumor, Arch. Int. Med. **28**:467 (Oct.) 1921.

there was a chain of these structures in the pelvis, each from 2 to 3 cm. in size; and in the other, metastases through various parts of the body.

Because of the unusual size and location of these structures in the following case, it is considered worthy of report.

REPORT OF CASE

History.—The patient (69942), aged 14 years, was admitted to the Jewish Hospital in the service of S. R. Blatteis, Dec. 22, 1921. Her condition was desperate, and she died within an hour after admission. The history obtained was unsatisfactory and had no bearing on the findings.

Postmortem Protocol.—The cadaver was that of a young female, 4 feet 2 inches tall, well developed and well nourished. Opening the thoracic cavity revealed, in the region of the thymus gland, more than twenty varying sized, irregularly shaped, purplish-red, soft masses which appeared collapsed. They were situated in the anterior superior mediastinum and surrounded the ascending portion and arch of the aorta. They were embedded in loose areolar tissue and had a generous blood supply. The largest was 34 by 10 by 8 mm. in size; the

Figure 2

Figure 3

Fig. 2.—Hemal nodes; natural size.

Fig. 3.—Hemal nodes; natural size; cross section.

smallest was scarcely visible to the naked eye. They varied much in shape, some were spherical, others elliptical, and still others were of a splenic form, with a distinct hilum and lobulations. They were arranged in groups supported by a mass of loose areolar and adipose tissue and were joined to one another by rather large blood vessels. One group was intimately attached by large tributaries to a big vein which entered the superior vena cava. They were all purplish in color with a covering that was smooth and glistening excepting at the part which might be called the hilum and to which the blood vessels were attached. Their consistency was very soft and they felt as though they had been emptied of their contents, the impression being very different than that gained from the palpation of the congested lymph nodes.

Macroscopic Appearance.—On section, the individual bodies were surrounded by a distinct thick capsule from which trabeculae arose to traverse the parenchyma, but no lobular divisions in most were discernible. The cut surface presented a spongy appearance and was also of a deep purplish color; small dewdrop bodies resembling malpighian corpuscles could be seen in a few areas. The material scraped from the surface was deep purple and apparently consisted mostly of blood.

Fig. 4.—Hemal node, showing trabeculae from capsule; large blood sinuses. ×200.

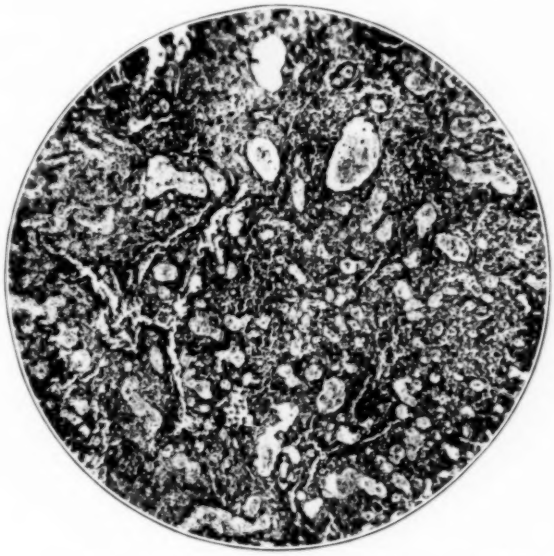

Fig. 5.—Hemal node; numerous various sized vascular channels; diffuse arrangement of lymphoid cells. ×100.

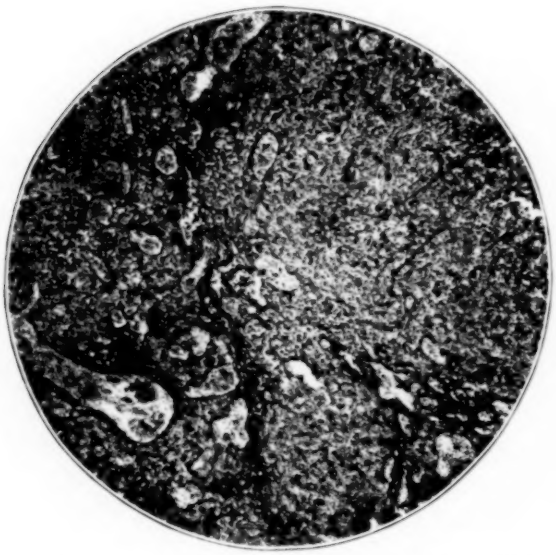

Fig. 6.—Hemal node showing large sinus with connective tissue fibrils (a). Van Giesen stain. ×100.

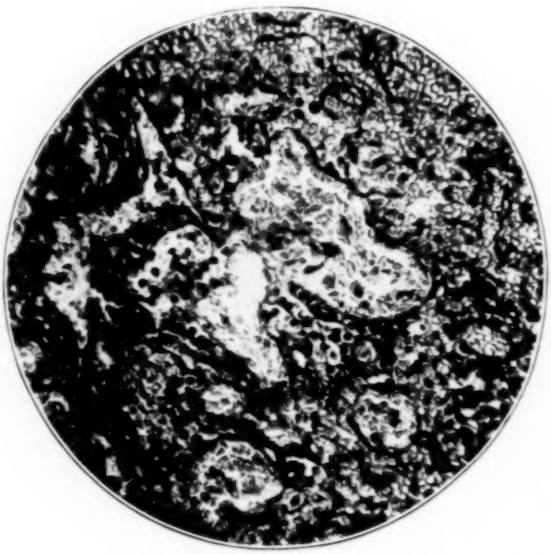

Fig. 7.—Hemal node; general arrangement of sinuses and contents. ×570

Microscopic Examination.—Sections were stained by hematoxylin-eosin, Van Giesen and Weigert's elastic tissue methods. Examination under low power reveals a mixture of highly vascular tissue and a number of small round cell collections supported by a variable amount of connective tissue stroma. The tissue is enclosed in a thin capsule composed of a few strands of fibrous connective tissue. From this capsule numerous thin fasciculi penetrate into the depths of the gland, some carrying blood vessels within the bundles. Scattered within some, there are a few collections of small round cells; neither elastic tissue nor the smooth muscle can be demonstrated within the capsule. Lying immediately beneath the capsule are many blood sinuses filled mostly with red blood cells and a few white cells. The remainder of the gland is divided up into varying sized alveoli by rather dense fibrous connective tissue partitions. These spaces are irregular in size and shape, assuming mostly a spherical outline.

The trabeculae are composed of bundles of connective tissue fibers arranged in an irregular fashion and interlacing. The fibers consist of long slender cells containing a few elliptical nuclei, some bundles showing beginning hyalinization. With the Van Giesen stain numerous fibrils arising from these trabeculae are seen to penetrate to within the body of the lobule and there form a connective tissue framework, subdividing the lobule into numerous small spaces (Fig. 8). These small spaces also vary in size and shape, being mostly circular. The reticulum is built up apparently from the connective tissue fibrils above described, the spaces actually being lined by flat endothelium. The reticular fibers form walls which are common to adjoining spaces. No elastic tissue or muscle could be demonstrated in these structures. The content of the spaces is blood. Within a few of these spaces are dense collections of small round cells resembling small lymphocytes. These collections are penetrated by small vascular channels in an irregular fashion. In only a very few can a definite reticulum be demonstrated by Van Giesen stain within the bodies of the follicles.

Although they resemble the follicles of lymph nodes, no germinal center or lymph sinuses could be demonstrated. Within the body of these collections are scattered also a few large polyhedral cells containing a large chromatic nucleus, and within the protoplasm numerous pigment granules; they resemble macrophages. The distribution and arrangement of the small round cells vary considerably, according to the part of the node examined, although relatively large groups are sometimes seen. In no part does the lymphoid element preponderate. The striking feature of all the sections is the predominant presence of the vascular element; in fact, in some places individual sinuses occupy the areas of several fields under low power magnification, and can easily be seen with the naked eye.

Careful study of numerous sections failed to reveal any evidence of red blood cell destruction. In most instances the red blood cells are intact and of normal shape and size; there are none of the evidences of red cell phagocytosis or lysis, as usually seen in the spleen. The resemblance to splenic structure is not as close as that described by other observers. There is nothing in the specimen that resembles splenic pulp. The distribution and the character of the connective tissue framework is entirely different and the vascular architecture is in no way comparable to that of the spleen. As a whole, the picture is that of a tissue composed of varying sized vascular channels supported by connective tissue reticulum. These channels divide and subdivide until they form either spaces or sinuses formed of a single layer of fibrous connective tissue and lined by a layer of endothelium. Together with this vascular tissue there are small round cells arranged either in organized groups distantly resembling lymph follicles, or diffusely scattered throughout the connective tissue stroma.

Evidences of red blood cell destruction were thoroughly searched for with the means available, but could not be demonstrated. On the contrary, as before stated, the red cells seem to present an unusual picture of preservation and in

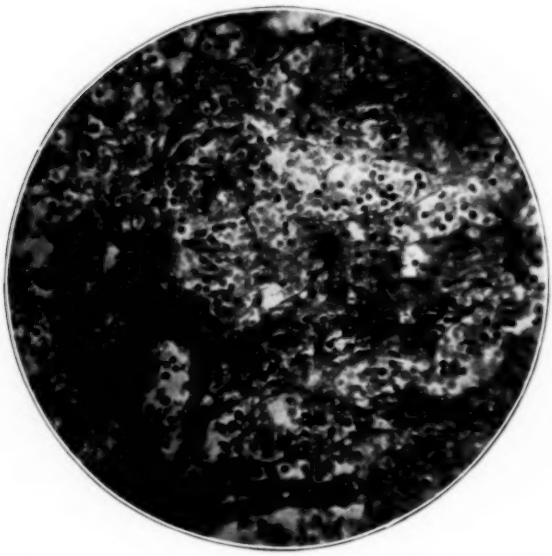

Fig. 8.—Hemal node; detail of smallest sinuses. ×570.

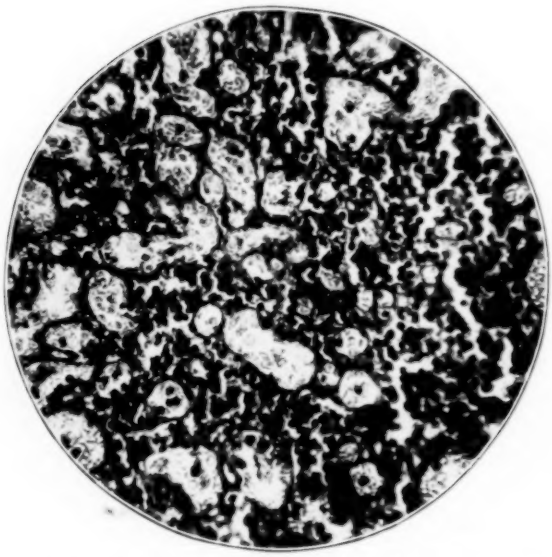

Fig. 9.—Hemal node, area showing relation of lymphoid cells to blood sinuses. ×420.

addition there were noted a few red cells which appear to be nucleated. Unfortunately, because of the method of fixation, special blood stains could not be made. Also, because of the early death of the patient blood studies could not be made. For these reasons this phase of the case could not be studied completely. However, the impression gained from a study of the specimen would be more likely to lead to the conclusion that the picture is certainly not that of a blood destroying organ, but rather that it has to do with blood formation.

In the able description by Warthin he states that the capsule and trabeculae contain smooth muscle and elastic fibers. In our specimen the most diligent search failed to reveal the presence of either of these elements. Perhaps, we must regard this fact as a sign of variation from the normal histology of the node, or as an evidence of pathology.

The remainder of the necropsy showed a very advanced mitral stenosis with the usual pathologic changes incident to the disease; chronic passive congestion of the lungs, liver, spleen and kidneys.

Comment.—The pathology of hemal nodes has received but scant attention in the literature. The only references available are those of Warthin who mentions changes in these structures, particularly in connection with the blood diseases such as pernicious anemia, leukemia, and Hodgkin's. Symmers reports two cases of neoplasm arising from these structures, one with metastases.

With the incomplete data at hand regarding the history of this case, there is no indication of disease of any sort, excepting that the patient had acute anterior poliomyelitis at 2 years of age. She was perfectly well, attending school up to about a week before admission, when after exposure to inclement weather she was suddenly taken ill and went to bed. She was not treated by a physician and on response to an ambulance call, the intern found her lying in bed in critical shape. She died of cardiac decompensation. It seems hardly likely that the presence of the nodes contributed in any way to the attack which ended her life. In other words, enlargement of these structures could not be explained by compensatory hyperplasia, to which Warthin calls attention in the disturbances of the hematopoietic system. The presence of these masses can then be explained only on one or two bases, either a congenital anomaly or a neoplastic hypertrophy. Examination of the specimen from the standpoint of a neoplasm fails to reveal any evidence of malignancy. There are no evidences of metaplasia, nor were there, after careful search, any metastases.

In addition to the unusual size, the rather unusual location of the nodes must be considered. All observers agree that the most common site of these structures is in prevertebral fat.[4] The only mention of anterior mediastinal growths is that of Symmers' metastatic growths.

4. Vincent and Harrison: J. Anat. & Physiol. **11**:176, 1897. McCallum: Textbook of Pathology, 1920, Ed. 2, p. 820.

We have, then, to deal with an abnormal increase in size in an unusual location of tissue corresponding to the descriptions of hemal nodes. I am inclined to regard this collection of structures rather in the light of a benign neoplastic hypertrophy of the hemolymph nodes than that of an anomaly. Symmers calls his malignant tumor a primary hemangiolymphoma and regards it as a malignant neoplasm. If the conclusion in this case is correct, similar tumors of benign nature exist.

STUDIES ON THE DETOXIFICATION OF CYANIDS

I. SOME FACTORS INFLUENCING THE DETOXIFICATION OF CYANIDS IN HEALTH AND DISEASE *

MEYER BODANSKY, M.A.
WITH THE COOPERATION OF
MOISE D. LEVY, M.D.
GALVESTON, TEX.

In a recent publication, Sullivan and Dawson [1] present data indicating that the sulphocyanate content of the saliva is lower in pellagrins than in normal persons. These authors found that in the active stage of the disease, when the patients are in a more or less cachetic condition, the potassium sulphocyanid (KSCN) formation is low. Sullivan and Dawson suggest that the increased production of potassium sulphocyanid during the convalescent stage of pellagra is due to better assimilation, a higher protein metabolism, and presumably a greater detoxifying power of the system as a whole. They state: "Thus the work herein oulined shows that the increased production of sulphocyanate is not closely bound up with total nitrogen but is more probably a product of some endogenous activity perhaps of the synthetic, detoxifying activity of the liver, coupled with a greater assimilation of sulphocyanogetic complexes."

It has been shown by Grober [2] that the excretion of sulphocyanate is very slight in cachetic or sick persons. This is obviously associated with a diminished absorption of foods. In the prognosis of gastric carcinoma, Fenwick [3] regards the total disappearance of potassium sulphocyanate from the saliva as a grave symptom. The main factor responsible for the diminution in the sulphocyanate concentration of the saliva in this condition, apparently, is due likewise to the impairment of the digestive and absorptive functions. Fenwick considers the formation of potassium sulphocyanate to be dependent also on the metabolic activity of the hepatic cells. He states that derangements in the function of the liver, as in phosphorus poisoning, acute yellow atrophy, and diffuse cirrhosis, are always accompanied by a diminished elimination of sulphocyanates. Finally, in functional disorders of the salivary glands, the sulphocyanate content of the saliva is lowered.

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* From the Laboratory of Biological Chemistry with the cooperation of the Department of Internal Medicine, University of Texas School of Medicine.

1. Sullivan, M. X., and Dawson, P. R.: J. Biol. Chem. **45**:473, 1921.
2. Grober, J. A.: Deutsch. Arch. klin. Med. **49**:243, 1901.
3. Fenwick, S., and Fenwick, W. S.: Cancer and Other Tumors of the Stomach, London, 1902, pp. 139, 229.

Sulphocyanates are very probably formed as a result of the detoxification of cyanids, either ingested as such, or arising in metabolism. According to Gies and Kahn,[4] and Gies, Lieb and Kahn,[5] the administration to dogs of alanine, glycocol, and leucine, is followed by an increased production of sulphocyanate. Willianen[6] found that the ingestion by rabbits of glycocol, creatinin, creatin and adenin causes an increase in the urinary excretion of sulphocyanates. That acetonitrile, madelic acid nitrile, and similar substances are rapidly converted into thiocyanates has been shown by Lang[7] as well as by Gies and his collaborators. On the other hand, Dezani's[8] investigations on the genesis of thiocyanic acid lead him to the conclusion that the sulphocyanic acid (HCNS), normally excreted by animals, is exogenous in origin. He asserts that only a minute fraction of ingested aliphatic nitriles are capable of conversion into sulphocyanate in the animal organism.

The view expressed by Gscheidlen[9] that sulphocyanic acid is formed in the salivary glands has been questioned by later investigators. Gies considers the salivary glands organs of excretion rather than of secretion. According to this author, the liver is the organ chiefly concerned in the production of sulphocyanate. The earlier investigation of Pascheles[10] demonstrated that the formation of sulphocyanic acid is not limited to the liver. In a number of "in vitro" experiments, it was found that muscle tissue, though less active than liver, likewise was capable of transforming sodium cyanid into sodium sulphocyanate.

Disease is frequently associated with metabolic derangements. For example, abnormal sugar tolerance curves are obtained in a large variety of pathologic conditions. Apparently, this is due to an impairment of the "carbohydrate disposal mechanism" of the body. The possibility suggests itself that in disease other metabolic functions might be similarly affected. If this were true in the case of the cyanid detoxifying function, it would account partially for the low sulphocyanate elimination in disease conditions. An analysis of Sullivan and Dawson's data shows that the average sulphocyanate content of saliva collected in 30 minutes from twenty-one active pellagrins is 1.36 mg. The average elimination of twenty-six convalescent pellagrins was found to be 2.55 mg. Five normal subjects eliminated on an average

4. Gies, W. J., and Kahn, M.: Dental Cosmos **55**:40, 1913.
5. Gies, W. J.; Lieb, C. C., and Kahn, M.: Dental Cosmos **56**:175, 1914.
6. Willianen, K.: Biochem. Ztschr. **1**:129, 1906.
7. Lang, S.: Arch. exper. Path. u. Pharmakol. **34**:247, 1894.
8. Dezani, S.: Arch. farm. sper. **23**:245, 1917; **24**:113, 193, 1918; **25**:83, 278, 1918; **26**:257, 1919; **27**:134, 1919; **28**:23, 1919.
9. Gscheidlen, cited in Abderhalden, Textbook of Physiological Chemistry, New York, 1911, p. 250.
10. Pascheles, W.: Arch. exper. Path. u. Pharmakol. **34**:281, 1894.

1.78 mg. potassium sulphocyanate (KCNS) in thirty minutes. A number of objections may be raised concerning the validity of conclusions based on the analysis of individual saliva specimens. Daily variations in the sulphocyanate elimination may be quite large. As is well known, smokers excrete greater quantities of thiocyanates than nonsmokers. In Sullivan and Dawson's work there is no indication as to which of the subjects were smokers and which were nonsmokers. It is also to be noted that some of the individuals in the active pellagra group eliminated more sulphocyanate than some of the normals.

In undertaking the present study, our object was to determine whether in disease there is an impairment in the cyanide detoxifying capacity of the organism. As far as we are aware, no functional test has been suggested hitherto for the determination of "cyanid tolerance." The principle of our method is based on the fact that the administration of small doses of potassium cyanid (KCN) results in a rapid increase in the sulphocyanate concentration of the saliva. It is appreciated that the salivary glands are not the only organs concerned in the excretion of sulphocyanate. This substance is excreted also in the urine and bile. Furthermore, the "salivary gland threshold" for sulphocyanates appears to be a peculiarity of the individual. Unless the excretory capacity of the salivary glands is determined adequately, it may be expected that analyses, only of the saliva, would afford insufficient data on which to base any deductions regarding the detoxifying capacity of the organism.

The excretion of sulphocyanates in the saliva after potassium cyanid administration is dependent on the following factors: absorption of the cyanid from the alimentary canal; the capacity of the organism to detoxify the cyanid—radicle; the functional capacity of the salivary glands in excreting potassium sulphocyanate. The first factor may be omitted from consideration because it is known that small quantities of cyanids are absorbed from vascular tissues with extreme rapidity. Furthermore, there is no reason for assuming that different individuals would show significant variations in this respect. If the third factor is controlled by determining the increased salivary elimination of potassium sulphocyanate after its ingestion as such, it becomes possible to study the second factor, namely, the cyanide detoxifying capacity of the organism.

METHODS

Accordingly, we adopted the following procedure. On the first day of the test, the subject, after rinsing the mouth with water, collected a specimen of saliva, under the stimulus of chewing white paraffin wax, during a fifteen minute period (from 7:45 to 8 a. m.). At 8 a. m., a gelatin capsule, containing 15 mg. potassium sulphocyanate, was

swallowed, and the mouth again rinsed with water. Specimens of saliva were collected, as before, during the following intervals: from 8:15 to 8:30; from 9 to 9:15; from 9:45 to 10, and from 11 to 11:15. No food was eaten before or during the test and the subjects abstained from tobacco. The sulphocyanate content of each saliva specimen was determined, the analyses being made in duplicate.

On the second day of the test, an initial specimen of saliva was again collected between 7:45 and 8 a. m. At 8 a. m. a gelatin capsule, containing 10 mg. of potassium cyanid, was swallowed. If 10 mg. of potassium cyanid were totally converted into potassium sulphocyanate, approximately 15 mg. of potassium sulphocyanate would be formed. Additional saliva specimens were collected during the same intervals as on the first day. For our purposes, it was not necessary to control the diet of the subjects. However, about the same type and quantity of food was eaten during the days of the test.

In the determination of sulphocyanates, an attempt was made first to use the Rupp-Schied [11]-Thiel [12] method as employed by Sullivan and Dawson.[1] This procedure proved too tedious. In the case of saliva specimens of low potassium sulphocyanate concentration, the method was inadequate. The sulphocyanate content of saliva can be determined with a fair degree of precision as well as with relative ease by means of the color reactions with ferric chlorid and hydrochloric acid. In our work, all the specimens collected from a given individual during the day were analyzed simultaneously. In this way it was possible to compare each specimen not only with standard potassium sulphocyanate solutions, but with each other as well.

A stock standard solution was prepared by dissolving 1 gm. of dry, pure potassium sulphocyanate in two liters of water. The standard solutions were prepared by diluting the stock solution (1 c.c. = 0.5 mg. KCNS), to suitable volumes. Standard solutions of the following concentrations were prepared:

1. Five c.c. stock solution diluted to 50 c.c. (5 c.c. = 0.25 mg.).
2. One c.c. stock solution diluted to 25 c.c. (5 c.c. = 0.10 mg.).
3. One c.c. stock solution diluted to 50 c.c. (5 c.c. = 0.05 mg.).
4. One c.c. stock solution diluted to 100 c.c. (5 c.c. = 0.025 mg.).
5. One c.c. stock solution diluted to 200 c.c. (5 c.c. = 0.0125 mg.).

From these standards it is possible to prepare other standard solutions whenever needed. For example, dilution of standard No. 2 with water in the proportion of 3:2 gives a solution, 5 c.c. of which is equivalent to 0.06 mg. The colorimetric comparisons were performed as follows: To 5 drops of 5 per cent. ferric chlorid and 4 drops of 1

11. Rupp, E., and Schied, A.: Ber. chem. Gesellsch. **35**:2191, 1902.
12. Thiel, A.: Ber. chem. Gesellsch. **35**:2766, 1902.

per cent. hydrochloric acid, in a 150 c.c. casserole, 5 c.c. of filtered saliva were added. After mixing, the color produced was compared with that obtained by adding standard potassium sulphocyanate solutions to similar quantities of ferric chlorid and hydrochloric acid. This method has proved itself to be entirely adequate for the purposes of this investigation. In view of the fact that substances interfering with the color reaction, such as salicylates, were excluded, no error from this source was possible. Interference due to aceto-acetic acid was not observed in any of the several hundred analyses performed by us. Nevertheless, as an additional measure of precaution, several drops of mercuric chlorid were added before discarding the solutions. The color due to ferric sulphocyanate ($Fe[CNS]_3$) is readily dispelled in this way.

In the present investigation, the test was applied to eight normal subjects (medical students) and seventeen patients, including three pellagrins. The results are recorded in Table 1. Examination of the data reveals the fact that the capacity to detoxify small amounts of potassium cyanid was not impaired in the pathologic conditions studied by us. It is to be noted that variations in the initial sulphocyanate concentration of the saliva may occur in the same individual from day to day. As a rule, the elimination of potassium sulphocyanate after potassium cyanid administration approximates that after potassium sulphocyanate ingestion. The rapidity with which potassium cyanid is transformed in the organism is very striking. Within fifteen minutes after the ingestion of this substance, it is absorbed, detoxified, and its elimination in the saliva becomes apparent. In this connection it is to be noted that one of the normal subjects (Lep.) showed an unusual delay in the detoxification of potassium cyanid.

The necessity for determining the excretory capacity of the salivary glands is emphasized by the results obtained in the test on another normal subject (Ram.). In this case, the initial sulphocyanate concentration was 1.8 mg. in 100 c.c. After the ingestion of 15 mg. potassium sulphocyanate, the maximum increase was obtained in the interval (from 8:15 to 8:30). The potassium sulphocyanate concentration of the saliva was now 2.2 mg. in 100 c.c., an increase of only 0.4 mg. A similar increase was obtained after the ingestion of 10 mg. potassium cyanid. In this instance, the highest concentration was reached during the interval from 9 to 9:15. In view of this and other findings, it appears that like dosages of potassium sulphocyanate or potassium cyanid do not necessarily stimulate equivalent excretory activity on the part of the salivary glands of different persons. We believe that this is one of the chief factors responsible for the wide variation in the sulphocyanate concentration of the saliva in man.

TABLE 1.—Data Showing the Effect of Potassium Sulphocyanate and Potassium Cyanid Administration on the Sulphocyanate* Concentration of the Saliva

Subject	Time, A. M.	First Day Influence of KCNS			Second Day Influence of KCN		
		KCNS Ingested, Mg.	Volume Saliva, C.c.	KCNS in 100 C.c. Saliva, Mg.	KCN Ingested, Mg.	Volume Saliva, C.c.	KCNS in 100 C.c. Saliva, Mg.
Whit.	7:45- 8:00	..	39	0.70	..	36	1.10
Normal	8:00	15	..	....	10	..	....
(Smoker)	8:15- 8:30	..	40	2.00	..	26	2.20
Male	9:00- 9:15	..	32	2.20	..	45	1.72
	9:45-10:00	..	47	1.80	..	44	1.60
	11:00-11:15	..	38	1.40	..	40	1.80
Mil.	7:45- 8:00	..	33	1.40	..	29	1.40
Normal	8:00	15	..	....	10	..	....
(Nonsmoker)	8:15- 8:30	..	36	1.56	..	23	1.90
Male	9:00- 9:15	..	34	1.90	..	23	2.00
	9:45-10:00	..	30	1.90	..	28	1.60
	11:00-11:15	..	27	2.40	..	22	1.60
Lit.	7:45- 8:00	..	30	2.60	..	22	4.00
Normal	8:00	15	..	....	10	..	....
(Smoker)	8:15- 8:30	..	23	3.00	..	24	5.00
Male	9:00- 9:15	..	19	3.50	..	16	5.50
	9:45-10:00	..	19	3.75	..	18	5.00
	11:00-11:15	..	18	3.30	..	26	4.00
Lep.	7:45- 8:00	..	21	3.00	..	15	2.70
Normal	8:00	15	..	....	10	..	....
(Smoker)	8:15- 8:30	..	24	4.00	..	16	2.50
Male	9:00- 9:15	..	25	4.00	..	52	2.50
Chronic constipation		..	37	4.00	..	39	3.50
		..	26	4.50	..	27	3.00
Ram.	7:45- 8:00	..	27	1.80	..	29	1.80
Normal	8:00	15	..	....	10	..	....
(Smoker)	8:15- 8:30	..	28	2.20	..	29	1.80
Male	9:00- 9:15	..	31	2.00	..	44	2.20
	9:45-10:00	..	29	2.00	..	46	2.00
	11:00-11:15	..	33	2.00	..	33	1.80
Ada.	7:45- 8:00	..	38	4.00	..	40	4.00
Normal	8:00	15	..	.. ..	10	..	....
(Smoker)	8:15- 8:30	..	40	4.00	..	39	4.00
Male	9:00- 9:15	..	35	4.40	..	39	5.00
	9:45-10:00	..	32	4.40	..	40	5 00
	11:00-11:15	..	25	4.40	..	28	4.50
Guy.	7:45- 8:00	..	55	1.30	..	45	2.00
Normal	8:00	15	..	....	10	..	....
(Nonsmoker)	8:15- 8:30	..	52	1.44	..	37	2.70
Male	9:00- 9:15	..	56	1.40	..	41	2.92
	9:45-10:00	..	49	1.68	..	48	2.20
	11:00-11:15	..	48	2.00	..	40	2.40
Col.	7:45- 8:00	..	67	0.44	..	61	0.80
Normal	8:00	15	..	....	10	..	....
(Nonsmoker)	8:15- 8:30	..	52	0.56	..	60	0.84
Male	9:00- 9:15	..	56	0.56	..	58	1.06
	9:45-10:00	..	50	0.74	..	50	1.06
	11:00-11:15	..	57	0.74	..	46	1.10
Cole.	7:45- 8:00	..	7.5	0.80	..	7.5	1.39
Pellagra	8:00	15	..	....	10	..	....
Convalescent	8:15- 8:30	..	10.0	1.40	..	13.0	2.15
(Nonsmoker)	9:00- 9:15	..	8.0	2.60	..	6.0	4.75
Female	9:45-10:00	..	6.5	2.40	..	13.0	3.23
	11:00-11:15	..	7.0	2.00	..	10.0	3.20
Rob.	7:45- 8:00	..	47	0.30	..	53	0.30
Pellagra,	8:00	15	..	....	10	..	....
arthritis	8:15- 8:30	..	41	0.40	..	42	0.34
(Smoker)	9:00- 9:15	..	54	0.42	..	48	0.50
Male	9:45-10:00	..	51	0.80	..	47	0.60
	11:00-11:15	..	40	0.70	..	42	0.76

* It is probable that the sulphocyanate occurring in the body is not entirely in the form of the potassium salt. For convenience, however, all results have been computed in terms of potassium sulphocyanate.

TABLE 1.—Data Showing the Effect of Potassium Sulphocyanate and Potassium Cyanid Administration on the Sulphocyanate Concentration of the Saliva—(*Continued*)

Subject	Time, A. M.	First Day Influence of KCNS			Second Day Influence of KCN		
		KCNS Ingested, Mg.	Volume Saliva, C.c.	KCNS in 100 C.c. Saliva, Mg.	KCN Ingested, Mg.	Volume Saliva, C.c.	KCNS in 100 C.c. Saliva, Mg.
Cal.	7:45– 8:00	..	10	0.40	..	8	0.40
Active pellagra	8:00	15	..	....	10	..	....
(Smoker)	8:15– 8:30	..	7	1.80	..	9	0.80
Male	9:00– 9:15	..	10	1.20	..	5	1.12
	9:45–10:00	..	7	0.60	..	4	1.12
	11:00–11:15	..	7	0.80	..	4.5	1.00
Joh.	7:45– 8:00	..	60	0.32	..	45	0.44
Arthritis,	8:00	15	..	....	10	..	....
pellagra 2 years	8:15– 8:30	..	34	0.44	..	43	0.92
ago	9:00– 9:15	..	45	0.96	..	39	1.20
(Nonsmoker)	9:45–10:00	..	60	0.88	..	46	1.20
Female	11:00–11:15	..	35	1.00	..	30	1.50
Web.	7:45– 8:00	..	22	1.80	..	38	1.80
Pernicious	8:00	15	..	....	10	..	....
anemia	8:15– 8:30	..	14	2.00	..	20	2.20
(Nonsmoker)	9:00– 9:15	..	13	4.40	..	14	4.80
Male	9:45–10:00	..	23	2.80	..	16	5.00
	11:00–11:15	..	8	2.80	..	13	3.60
Dal.†	7:45– 8:00	..	18	0.55	..	10	2.00
Pernicious	8:00	15	..	....	10	..	....
anemia	8:15– 8:30	..	14	0.55	..	14	3.20
(Smoker)	9:00– 9:15	..	12	0.65	..	18	4.00
Male	9:45–10:00	..	12	1.00	..	5	4.40
	11:00–11:15	..	19	0.80	..	18	4.00
Amun.	7:45– 8:00	..	13	0.60	..	10	1.30
Leprosy	8:00	15	..	....	10	..	....
Female	8:15– 8:30	..	28	2.40	..	23	1.80
	9:00– 9:15	..	23	2.40	..	20	2.90
	9:45–10:00	..	22	1.70	..	27	2.40
	11:00–11:15	..	21	1.70	..	27	2.60
Godd.	7:45– 8:00	..	25	1.50	..	33	2.00
Leprosy	8:00	15	..	....	10	..	....
(Smoker)	8:15– 8:30	..	41	2.20	..	33	2.80
Male	9:00– 9:15	..	40	2.40	..	50	3.40
	9:45–10:00	..	37	2.40	..	31	3.00
	11:00–11:15	..	37	2.00	..	41	2.80
Cort.	7:45– 8:00	..	37	2.00	..	20	2.40
Leprosy	8:00	15	..	....	10	..	....
Female	8:15– 8:30	..	25	2.80	..	30	4.20
	9:00– 9:15	..	25	3.70	..	16	3.40
	9:45–10:00	..	30	3.30	..	37	3.40
	11:00–11:15	..	38	3.00	..	30	3.30
How.	7:45– 8:00	..	38	0.40	..	36	0.50
Congestion of	8:00	15	..	....	10	..	....
liver, passive	8:15– 8:30	..	41	0.64	..	31	0.80
(Smoker)	9:00– 9:15	..	25	0.70	..	45	1.40
Male	9:45–10:00	..	24	0.64	..	35	1.90
	11:00–11:15	..	33	0.70	..	30	1.80
Val.	7:45– 8:00	..	34	1.60	..	28	1.80
Congestion of	8:00	15	..	....	10	..	....
liver, passive	8:15– 8:30	..	34	1.84	..	31	2.00
Female	9:00– 9:15	..	35	2.20	..	29	2.60
	9:45–10:00	..	34	2.80	..	27	3.00
	11:00–11:15	..	30	3.60	..	28	3.60
O'Br.	7:45– 8:00	..	26	0.56	..	15	1.10
Cholangitis,	8:00	15	..	....	10	..	....
acute, arsenical	8:15– 8:30	..	31	0.96	..	38	1.20
(Smoker)	9:00– 9:15	..	46	0.60	..	35	1.40
Male	9:45–10:00	..	33	1.00	..	17	1.60
	11:00–11:15	..	43	1.10	..	52	1.20

† In this patient, the second day's test was applied one day following blood transfusion.

TABLE 1.—Data Showing the Effect of Potassium Sulphocyanate and Potassium Cyanid Administration on the Sulphocyanate Concentration of the Saliva—(*Continued*)

Subject	Time, A. M.	First Day Influence of KCNS			Second Day Influence of KCN		
		KCNS Ingested, Mg.	Volume Saliva, C.c.	KCNS in 100 C.c. Saliva, Mg.	KCN Ingested, Mg.	Volume Saliva, C.c.	KCNS in 100 C.c. Saliva, Mg.
Amel.	7:45– 8:00	..	21	1.00	..	18	2.40
Tuberculous peritonitis	8:00	15	..	....	10	..	....
Female	8:15– 8:30	..	22	1.80	..	17	2.40
	9:00– 9:15	..	25	3.50	..	31	3.00
	9:45–10:00	..	25	2.40	..	16	4.00
	11:00–11:15	..	24	2.00	..	16	3.00
Jac.	7:45– 8:00	..	30	0.80	..	23	0.55
Diffuse hepatic cirrhosis	8:00	15	..	....	10	..	....
(Smoker)	8:15– 8:30	..	11	2.60	..	20	0.80
Male	9:00– 9:15	..	6	2.60	..	9	2.60
	9:45–10:00	..	7	2.80	..	6	2.80
	11:00–11:15	..	13	1.10	..	15	1.40
Wil.	7:45– 8:00	..	30	2.00	..	28	2.70
Arthritis	8:00	15	..	....	10	..	....
(Nonsmoker)	8:15– 8:30	..	31	2.90	..	24	2.70
Male	9:00– 9:15	..	37	2.60	..	25	3.90
	9:45–10:00	..	28	2.80	..	28	3.60
	11:00–11:15	..	16	3.30	..	33	3.80
Norr.	7:45– 8:00	..	14	2.40	..	23	3.00
Diabetes	8:00	15	..	....	10	..	....
(Nonsmoker)	8:15– 8:30	..	14	2.20	..	40	2.00
Female	9:00– 9:15	..	22	4.00	..	34	3.00
	9:45–10:00	..	23	2.80	..	15	4.00
	11:00–11:15	..	31	2.00	..	31	2.00
Derr.	7:45– 8:00	..	31	3.20	..	22	3.40
Gastric carcinoma	8:00	15	..	....	10	..	....
Female	8:15– 8:30	..	30	3.20	..	23	4.60
	9:00– 9:15	..	21	5.00	..	24	3.60
	9:45–10:00	..	33	5.00	..	21	4.00
	11:00–11:15	..	32	4.00	..	26	4.40

Of especial interest are the results obtained in the case of one of the patients (Cal.), with acute pellagra, of the systemic type. The administration of 15 mg. of potassium sulphocyanate caused an increase from 0.4 to 1.8 mg. of potassium sulphocyanate in 100 c.c. of saliva. This was followed by a gradual decrease. On the other hand, the ingestion of 10 mg. of potassium cyanid produced an effect that was not quite as marked. This might be interpreted, perhaps, as an indication of a lowered detoxifying power. We do not believe, however, that the failure to transform the potassium cyanid rapidly was due to a disturbance in the detoxifying activity of the liver or of any other organ, but rather to a deficiency in available mercapto yielding substances. As will be shown in another connection, when the administration of potassium cyanid was preceded by the ingestion of 1 gm. of cystin, the patient exhibited a normal ability to detoxify cyanids.

In various hepatic disturbances, we failed to observe any abnormalities in cyanid tolerance. Significant is the fact that the patient with diffuse hepatic cirrhosis (Jac.) showed a normal capacity to convert potassium cyanid into sulphocyanate.

Table 2 and Chart 1 have been prepared for the purpose of summarizing the results thus far obtained and for comparing the response of sick and healthy persons to potassium sulphocyanate and potassium cyanid administration. The average initial sulphocyanate concentration was lower in the patients than in the normals. Fifteen minutes after the ingestion of 15 mg. of potassium sulphocyanate, there was an average increase of 0.44 mg. and 0.54 mg. of potassium sulphocyanate

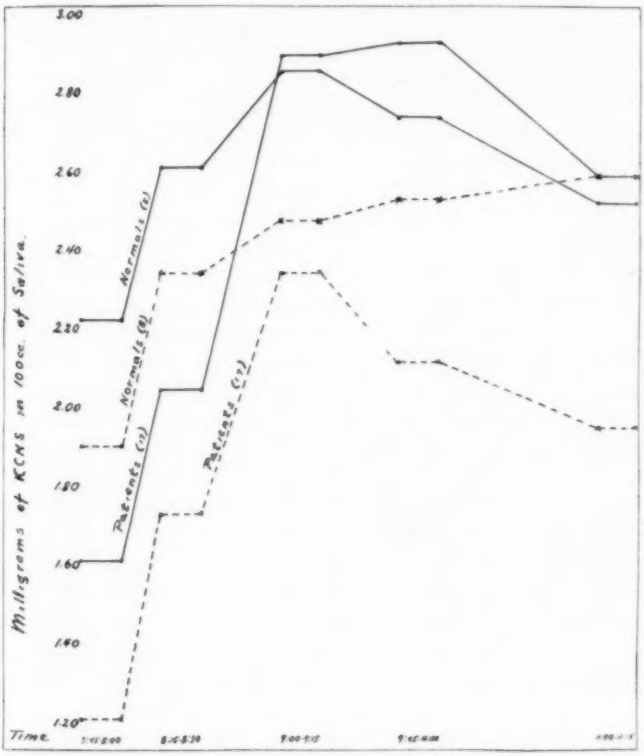

Chart 1.—The average curves showing the increased salivary excretion of sulphocyanate in normals and patients following the administration of potassium sulphocyanate and potassium cyanid. (Broken line—effect of potassium sulphocyanate; solid line—effect of potassium cyanid).

in 100 c.c. of the saliva of the healthy and sick persons, respectively. The ingestion of 10 mg. potassium cyanid caused, after fifteen minutes, an average increase of 0.39 mg. potassium sulphocyanate in 100 c.c. of the saliva of the eight normals. The average increased concentration in the saliva of the seventeen patients amounted to 0.43 mg. At the end

of one hour the average sulphocyanate concentration of the patients' saliva slightly exceeded that of the normals. From this it is to be concluded that in disease the low sulphocyanate elimination is ordinarily due, not to a derangement in the detoxifying capacity of the organism, but more likely to a lowered protein intake and metabolism.

A brief study was made to determine the influence of fatigue of the salivary glands on potassium sulphocyanate excretion. Schneider [13] has

TABLE 2.—DATA SHOWING THE RESPONSE OF SICK AND HEALTHY PERSONS TO POTASSIUM SULPHOCYANATE AND POTASSIUM CYANID ADMINISTRATION

Time	Influence of KCNS				Influence of KCN			
	KCNS Ingested, Mg.	KCNS in 100 C.c. Saliva			KCN Ingested, Mg.	KCNS in 100 C.c. Saliva		
		Normals (8)	Patients (17)	Total (25)		Normals (8)	Patients (17)	Total (25)
7:45– 8:00	..	1.91	1.22	1.44	..	2.23	1.62	1.81
8:00	15	....	....	....	10	....	....	....
8:15– 8:30	..	2.35	1.76	1.95	..	2.62	2.05	2.23
9:00– 9:15	..	2.48	2.35	2.39	..	2.86	2.90	2.82
9:45–10:00	..	2.53	2.12	2.25	..	2.74	2.93	2.87
11:00–11:15	..	2.50	1.95	2.16	..	2.52	2.59	2.57

TABLE 3.—DATA SHOWING THE PERIODIC VARIATION IN THE EXCRETION OF SULPHOCYANATE IN THE SALIVA

Subject	7:45-8:00		8:15-8:30		9:00-9:15		9:45-10:00		11:00-11:15		Remarks
	Vol. C.c.	Mg. in 100 C.c.	Vol. C.c.	Mg. in 100 C.c.	Vol. C.c.	Mg. in 100 C.c.	Vol. C.c.	Mg. in 100 C.c.	Vol. C.c.	Mg. in 100 C.c.	
Ram.	35	1.14	32	1.14	40	0.70	40	0.60	40	0.60	Normal
Gay.	41	1.80	41	1.80	38	1.80	47	1.20	42	1.20	Normal
Col.	50	0.50	55	0.40	42	0.40	74	0.30	61	0.30	Normal
Cal.	13	0.44	10	0.36	10	0.40	7.5	0.40	10	0.40	Pellagra
Web.	31	2.60	30	2.40	12	2.60	15	2.60	25	2.80	Pernicious anemia
Dal.	12	1.90	9	1.80	10	1.70	9	1.70	14	1.70	Pernicious anemia
Amun.	17	1.60	18	1.30	12	1.40	11	1.40	11	1.00	Leprosy
Cort.	31	2.20	43	2.00	39	2.30	45	2.00	30	2.00	Leprosy
Val.	28	2.10	26	2.10	27	2.30	26	2.20	27	2.20	Congestion of liver
How.	38	0.90	45	0.60	35	0.60	41	0.60	53	0.56	Congestion of liver
O'Br.	40	1.80	35	1.60	41	1.60	40	1.50	55	1.40	Cholangitis
Amel.	15	2.60	20	2.60	17	2.80	17	2.60	16	2.60	Tubere. peritonitis
Jne.	11	0.72	4	0.68	6	0.68	7	0.60	7	0.60	Dif. hepatic cirrho.
Wil.	35	2.60	47	2.70	46	2.60	30	2.60	35	2.40	Arthritis
Norr.	40	2.00	30	2.00	37	2.20	23	2.20	27	2.20	Diabetes
Derr.	15	3.00	30	3.00	25	2.90	22	3.00	34	3.00	Gastric carcinoma
Aver.	28.3	1.74	30.3	1.65	27.3	1.69	28.4	1.60	30.4	1.56	

shown that the excretion of sulphocyanate may be diminished considerably by prolonged stimulation of the salivary glands. In one case, the flow of saliva was continuously provoked by chewing paraffin. This resulted in a decrease of the potassium sulphocyanate concentration from 0.004 per cent. at 8:18 a. m. to 0.002 per cent. at 11 a. m. We have determined the periodic variation in the sulphocyanate elimination in the case of sixteen of the twenty-five subjects—three normals and thirteen patients. The saliva was collected during the same intervals as

13. Schneider, E. C.: Am. J. Physiol. **5**:276, 1901.

before, no food being taken on the morning of the test. The results (Table 3) show that usually the initial saliva specimen has a slightly greater potassium sulphocyanate concentration than the specimens collected during the subsequent time intervals. Nevertheless, it is clear that resting the glands aids in the maintenance of the potassium sulphocyanate concentration of the saliva at a fairly constant level.

Influence of Cystin Feeding on the Detoxification of Potassium Cyanid.—The formation of sulphocyanate in the body appears to be due to a conjugation of cyanid and mercapto groups. It seems that the most important factor is the metabolic supply of the cyanid—radicle. Gies, Lieb and Kahn [5] tested the effect of mercapto yielding substances, including cystin, on sulphocyanate production and distribution in the animal organism. Crude cystin was fed to a dog for seven days. This produced but an insignificant increase in the sulphocyanate content of the urine. However, the liver of the experimental animal was found to contain more potassium sulphocyanid than the livers of the control animals.

We have studied the effect of feeding pure cystin on the formation of sulphocyanate and the detoxification of potassium cyanid in three normal subjects and twelve patients. In determining the influence of cystin, the subject collected an initial specimen of saliva between 7:45 and 8 a. m. At 8 a. m., 1 gm. cystin, mixed with oatmeal or some other cereal, was ingested. Additional saliva specimens were collected during the intervals from 8:15 to 8:30; from 9 to 9:15; from 9:45 to 10, and from 11 to 11:15. On the following day, the effect of cystin on the detoxification of potassium cyanid was determined. An initial saliva specimen was collected again from 7:45 to 8. The cystin was ingested, as before, at 8 a. m. From 8:15 to 8:30, a second specimen of saliva was collected. At 8:45, 10 mg. of potassium cyanid were administered in a gelatin capsule. Three more saliva specimens were collected during the intervals from 9 to 9:15; from 9:45 to 10, and from 11 to 11:15. The results of the analyses of the saliva are recorded in Table 4.

The ingestion of cystin usually produced no effect on the sulphocyanate concentration of the saliva. In a number of subjects, however, there occurred, as a result of cystin feeding, a marked increase in sulphocyanate elimination. This appeared to be especially marked in the case of a convalescent pellagrin (Cole). If the administration of potassium cyanid is preceded by the ingestion of cystin, the output of sulphocyanate in the saliva is considerably increased. The effect is much more pronounced than that produced when potassium cyanid alone is administered. The averages computed from the results of these experiments are presented in Table 5 and Chart 2. It will be observed

TABLE 4.—Data Showing the Effect of Cystin Upon Sulphocyanate Excretion and Potassium Cyanid Detoxification

Subject	Time, A. M.	First Day Influence of Cystin			Second Day Influence of Cystin + KCN		
		Cystin Ingested, Gm.	Volume Saliva, C.c.	KCNS in 100 C.c. Saliva, Mg.	Cystin or KCN Ingested	Volume Saliva, C.c.	KCNS in 100 C.c. Saliva, Mg.
Whit.	7:45- 8:00	..	28	1.50	.....	30	1.90
Normal	8:00	1	..	....	1 gm.	..	....
Male	8:15- 8:30	..	33	1.60	.....	37	1.60
	8:45	..	..	....	10 mg. KCN	..	....
	9:00- 9:15	..	30	1.54	.....	32	3.20
	9:45-10:00	..	34	1.60	.....	34	3.10
	11:00-11:15	..	27	1.30	.....	38	1.60
Ram.	7:45- 8:00	..	27	1.70	.....	36	1.20
Normal	8:00	1	..	....	1 gm.	..	....
Male	8:15- 8:30	..	31	1.60	.....	27	1.04
	8:45	..	..	....	10 mg. KCN	..	....
	9:00- 9:15	..	40	1.60	.....	32	1.81
	9:45-10:00	..	46	1.60	.....	39	1.80
	11:00-11:15	..	45	1.52	.....	38	1.70
Guy.	7:45- 8:00	..	53	2.30	.....	44	2.00
Normal	8:00	1	..	....	1 gm.	..	....
Male	8:15- 8:30	..	44	2.30	.....	48	1.70
	8:45	..	..	....	10 mg. KCN	..	....
	9:00- 9:15	..	44	2.30	.....	43	3.10
	9:45-10:00	..	42	2.10	.....	46	3.00
	11:00-11:15	..	51	2.00	.....	42	2.40
Col.	7:45- 8:00	..	30	1.52	.....	7	3.86
Pellagra	8:00	1	..	....	1 gm.	..	....
Female	8:15- 8:30	..	16	1.52	.....	6	4.01
	8:45	..	..	....	10 mg. KCN	..	....
	9:00- 9:15	..	11	2.30	.....	7	8.37
	9:45-10:00	..	5	3.00	.....	6	5.00
	11:00-11:15	..	18	1.28	.....	11	5.18
Rob.	7:45- 8:00	..	47	0.44	.....	48	0.30
Pellagra,	8:00	1	..	....	1 gm.	..	....
arthritis	8:15- 8:30	..	44	0.44	.....	43	0.20
Male	8:45	..	..	....	10 mg. KCN	..	....
	9:00- 9:15	..	43	0.44	.....	45	0.56
	9:45-10:00	..	35	0.42	.....	43	0.76
	11:00-11:15	..	42	0.40	.....	43	0.54
Cal.	7:45- 8:00	..	7	0.60	.....	5	1.00
Pellagra	8:00	1	..	....	1 gm.	..	....
Male	8:15- 8:30	..	5	0.60	.....	12	0.60
	8:45	..	..	....	10 mg. KCN	..	....
	9:00- 9:15	..	5	0.48	.....	15	0.80
	9:45-10:00	..	6	0.72	.....	10	1.80
	11:00-11:15	..	5	0.72	.....	9	1.60
Joh.	7:45- 8:00	..	38	0.80	.....	25	0.60
Arthritis,	8:00	1	..	....	1 gm.	..	....
pellagra	8:15- 8:30	..	33	0.80	.....	28	0.60
2 years ago	8:45	..	..	....	10 mg. KCN	..	....
	9:00- 9:15	..	33	0.92	.....	21	1.88
	9:45-10:00	..	25	1.00	.....	33	1.80
	11:00-11:15	..	57	0.76	.....	49	1.75
Amun.	7:45- 8:00	..	8	1.60	.....	15	2.20
Leprosy	8:00	1	..	....	1 gm.	..	....
Female	8:15- 8:30	..	18	1.40	.....	16	1.80
	8:45	..	..	....	10 mg. KCN	..	....
	9:00- 9:15	..	18	1.50	.....	23	3.40
	9:45-10:00	..	15	1.50	.....	19	3.70
	11:00-11:15	..	17	1.20	.....	24	2.70
Godd.	7:45- 8:00	..	29	2.60	.....	30	2.40
Leprosy	8:00	1	..	....	1 gm.	..	....
Male	8:15- 8:30	..	35	2.60	.....	45	2.40
	8:45	..	..	....	10 mg. KCN	..	....
	9:00- 9:15	..	35	2.60	.....	45	3.60
	9:45-10:00	..	31	2.80	.....	43	3.80
	11:00-11:15	..	21	2.80	.....	30	3.50

TABLE 4.—Data Showing the Effect of Cystin Upon Sulphocyanate Excretion and Potassium Cyanid Detoxification—(*Continued*)

Subject	Time, A. M.	First Day Influence of Cystin			Second Day Influence of Cystin + KCN		
		Cystin Ingested, Gm.	Volume Saliva, C.c.	KCNS in 100 C.c. Saliva, Mg.	Cystin or KCN Ingested	Volume Saliva, C.c.	KCNS in 100 C.c. Saliva, Mg.
Cort.	7:45– 8:00	..	26	2.50	.....	40	2.20
Leprosy	8:00	1	..	....	1 gm.	..	....
Female	8:15– 8:30	..	33	2.50	.....	43	2.20
	8:45	..	..	....	10 mg. KCN	..	....
	9:00– 9:15	..	41	2.50	.....	25	3.00
	9:45–10:00	..	36	2.40	.....	25	4.40
	11:00–11:15	..	26	2.80	.....	27	4.00
How.	7:45– 8:00	..	27	0.80	.....	35	1.00
Congestion of	8:00	1	..	....	1 gm.	..	....
liver, passive	8:15– 8:30	..	44	1.00	.....	35	0.70
(Smoker)	8:45	..	..	....	10 mg. KCN	..	....
Male	9:00– 9:15	..	30	0.80	.....	34	0.80
	9:45–10:00	..	46	0.75	.....	42	1.20
	11:00–11:15	..	44	0.80	.....	27	1.50
Val.	7:45– 8:00	..	31	1.90	.....	28	2.00
Congestion of	8:00	1	..	....	1 gm.	..	....
liver, passive	8:15– 8:30	..	30	1.60	.....	26	2.00
Female	8:45	..	..	....	10 mg. KCN	..	....
	9:00– 9:15	..	26	1.40	.....	27	4.40
	9:45–10:00	..	50	1.40	.....	26	3.80
	11:00–11:15	..	21	1.50	.....	27	3.40
O'Br.	7:45– 8:00	..	37	2.00	.....	42	1.10
Cholangitis	8:00	1	..	....	1 gm.	..	....
(Smoker)	8:15– 8:30	..	25	1.00	.....	36	1.10
Male	8:45	..	..	....	10 mg. KCN	..	....
	9:00– 9:15	..	37	1.40	.....	40	1.90
	9:45–10:00	..	46	1.50	.....	45	1.50
	11:00–11:15	..	30	1.40	.....	52	1.50
Amel.	7:45– 8:00	..	14	2.60	.....	18	2.20
Tuberculous	8:00	1	..	....	1 gm.	..	....
peritonitis	8:15– 8:20	..	28	2.00	.....	23	2.00
Female	8:45	..	..	....	10 mg. KCN	..	....
	9:00– 9:15	..	18	2.50	.....	19	3.60
	9:45–10:00	..	18	2.60	.....	16	5.00
	11:00–11:15	..	12	3.00	.....	19	4.60
Norr.	7:45– 8:00	..	33	2.60	.....	28	2.00
Diabetes	8:00	1	..	....	1 gm.	..	....
Female	8:15– 8:30	..	30	2.00	.....	25	1.60
	8:45	..	..	....	10 mg. KCN	..	....
	9:00– 9:15	..	26	2.00	.....	25	2.70
	9:45–10:00	..	18	3.60	.....	32	3.80
	11:00–11:15	..	26	3.60	.....	10	4.80

TABLE 5.—Data Showing the Average Effect of Feeding Cystin on the Excretion of Sulphocyanate and the Detoxification of Potassium Cyanid

Time	Influence of Cystin				Influence of Cystin + KCN			
	Cystin Ingested Gm.	KCNS in 100 C.c. Saliva			Cystin or KCN Ingested.	KCNS in 100 C.c. Saliva		
		Normals (3)	Patients (12)	Total (15)		Normals (3)	Patients (12)	Total (15)
7:45– 8:00	....	1.83	1.66	1.70	....	1.73	1.74	1.74
8:00	1	....	....	....	1 gm.	....	....	....
8:15– 8:30	....	1.83	1.46	1.53	....	1.45	1.61	1.58
8:45	....	....	....	....	10 mg. KCN	....	....	....
9:00– 9:15	....	1.81	1.56	1.61	....	2.70	2.93	2.89
9:45–10:00	....	1.77	1.81	1.80	....	2.63	3.03	2.95
11:00–11:15	....	1.61	1.69	1.67	....	1.90	2.92	2.72

that in the case of the normal subjects, cystin produced no effect on the sulphocyanate excretion in the saliva. The gradual slight decrease in concentration was obviously due to fatigue of the salivary glands or to the removal of some potassium sulphocyanid from the circulation. In the patients the effect was somewhat different. The average potassium sulphocyanid concentration of the second specimen was lower than that

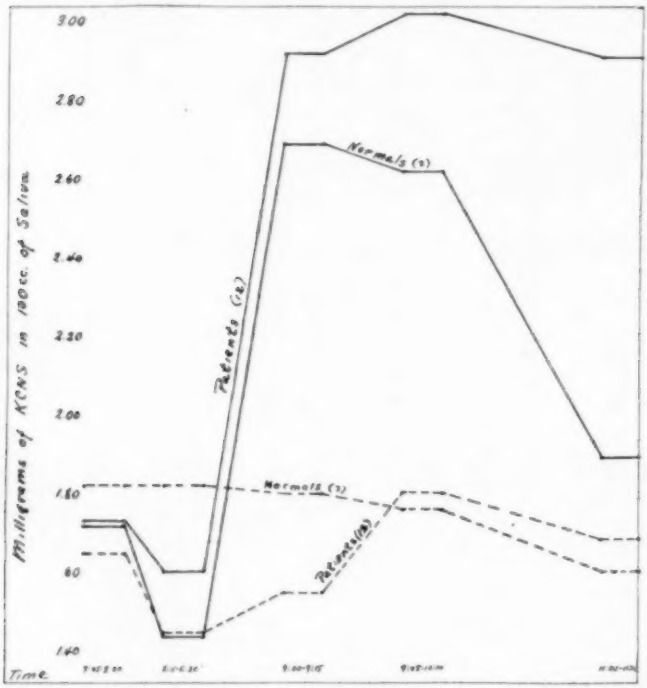

Chart 2.—The average curves showing the effect of feeding cystin (broken line) on the excretion of sulphocyanate in the saliva. The influence of cystin on the detoxification of potassium cyanid is represented by the solid lines.

of the initial saliva specimen. Then there followed a measureable increase, the maximum being reached during the interval from 9:45 to 10. The explanation suggesting itself is that the supply of sulphur yielding complexes before the administration of the cystin was insufficient to combine with all the available cyanid radicles. That in disease the cyanid detoxifying power remains unimpaired, provided the supply of cystin is adequate, is made clear by the results of our experiments in which both cystin and potassium cyanid were administered. As in the case of the tests with cystin alone, the potassium sulphocyanid

elimination, in some instances, was lower during the second time interval than during the first. Forty-five minutes were allowed for the partial absorption of the cystin. Ten milligrams of potassium cyanid were then swallowed. In this way an ample available supply both of cyanid and mercapto radicles was assured. Conjugation occurred rapidly, as is evident from the fact that the average potassium sulpho-

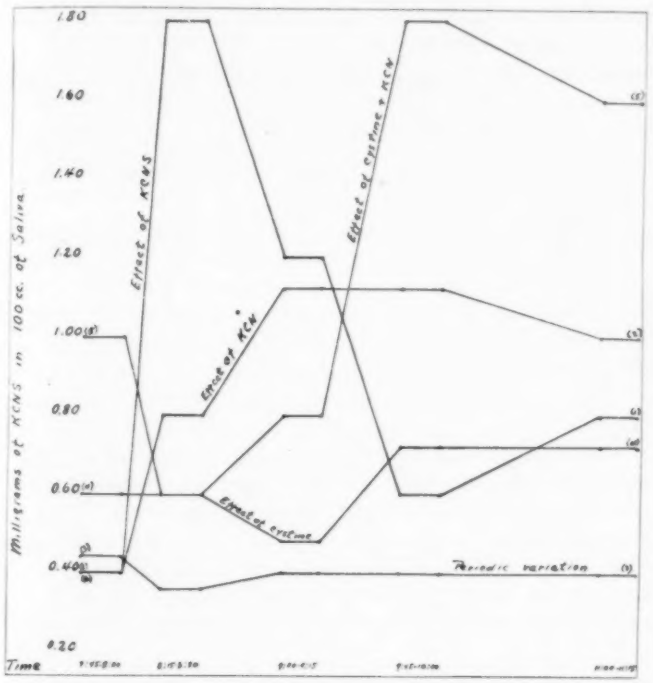

Chart 3.—The curves represent the results obtained in a study of the cyanid detoxifying capacity of one of the patients (Cal.) with an acute case of pellagra.

cyanid concentration of the saliva, collected from fifteen to thirty minutes after the administration of the potassium cyanid, was 83 per cent. greater than that of the preceding specimen.

It is hoped that this work will be extended to the study of other pathologic conditions. The researches of Reid Hunt [14] are of especial interest in this connection. This author found that the ingestion of thyroid by mice increased their resistance to acetonitrile. On the other hand, feeding mice with parathyroids caused a distinct increase of

14. Hunt, R.: J. Biol. Chem. **1**:33, 1905.

their susceptibility to acetonitrile. In determining cyanid detoxification in man, it is suggested that the five day test be employed. To insure a return to normal of the sulphocyanate content of the saliva on successive test days, the tests may be performed on alternate days or in the following order:

First Day.—Influence of potassium sulphocyanid (15 mg.) on sulphocyanate elimination.

Second Day.—Periodic variation in the elimination of potassium sulphocyanid in saliva.

Third Day.—Effect of potassium cyanid (10 mg.) on the sulphocyanate content of the saliva.

Fourth Day.—Effect of cystin (1 gm.) on sulphocyanate elimination.

Fifth Day.—Effect of cystin (1 gm.) on the detoxification of potassium cyanid (10 mg.).

In Chart 3 are represented the results of a five day test, performed on one of the patients (Cal.), an active pellagrin. It will be observed that the ingestion of potassium sulphocyanate produced a marked increase in the sulphocyanate concentration of the saliva. This effect was temporary, however. On administering 10 mg. potassium cyanid, the potassium sulphocyanate concentration increased about three times. The return to normal in this case was slow. The sulphocyanate concentration of the saliva remained practically constant when neither potassium sulphocyanate nor potassium cyanid were taken. Feeding 1 gm. cystin was followed, in this subject, by a slight increase in sulphocyanate elimination. When the administration of 10 mg. potassium cyanid was preceded by the ingestion of 1 gm. cystin, a rapid increase in the sulphocyanate concentration of the saliva was obtained. In this case the curve indicates a delayed return to the initial sulphocyanate concentration and, therefore, a marked degree of detoxification.

SUMMARY

1. The detoxification of potassium cyanid was determined in eight normal subjects and seventeen hospital patients.

2. Similar dosages of potassium sulphocyanate or potassium cyanid do not necessarily stimulate equivalent excretory activity on the part of the salivary glands of different persons.

3. The average sulphocyanate concentration of the saliva was found to be lower in the patients than in the normal subjects. However, after the ingestion of potassium sulphocyanate or potassium cyanid, the sulphocyanate concentration of the patients' saliva increased more rapidly than in the case of the normals.

4. Resting the salivary glands during the intervals indicated in our procedure, aids in maintaining the sulphocyanate concentration of the

saliva at a fairly constant level when neither potassium cyanid nor potassium sulphocyanate are administered.

5. In normal subjects, cystin produced no effect on the sulphocyanate excretion in the saliva. On the other hand, a slight increase in potassium sulphocyanate elimination was observed in some of the patients.

6. The detoxification of potassium cyanid occurs more rapidly in the human organism when the administration of the cyanid is preceded by the ingestion of cystin.

7. It appears from our results that in certain disease conditions, such as pellagra, the cyanid detoxifying power remains unimpaired, provided the supply of cystin is adequate.

8. A functional test is proposed for the determination of the "cyanid detoxifying capacity" in man.

STUDIES OF THE BLOOD GASES IN A CASE OF PAROXYSMAL TACHYCARDIA*

EDWARD P. CARTER, M.D., AND HAROLD J. STEWART, M.D.†
BALTIMORE

During the progress of some studies of the blood gases in auricular fibrillation and after the restoration of the normal sinus mechanism by quinidin sulphate, by one of the authors,[1] a case of paroxysmal tachycardia came under observation and studies of the blood gases were made during the paroxysm and after the return to the normal rate. Barcroft, Bock and Roughton [2] have reported the only similar studies, with an attempt to determine the rate of blood flow and the cardiac output during a paroxysm and in the presence of the normal sinus mechanism. They found in two attacks of paroxysmal tachycardia that the volume output of the heart per minute decreased from one-half to one-third of the normal value, while the ventricular output fell to one-sixth the normal amount. The degree of ischemia was particularly marked in the skin as shown by a marked discrepancy between the oxygen content of blood from the basilic vein and that of the mixed venous blood in the lungs. The depth of respiration was reduced by one-half, but the rate was approximately doubled. No reduction in oxygen saturation of the arterial blood was found. Meakins,[3] from animal experimentation, has concluded that tachycardia, whether regular or irregular, does not in itself produce a decrease in the oxygen saturation of the arterial blood, but that if the tachycardia induces failure of the circulation with pulmonary congestion or edema, a decrease of arterial oxygen saturation will occur.

It was thought of interest to add the studies made of this case to the literature, because the conclusions drawn differ somewhat from those of Barcroft, Bock and Roughton.

METHODS

The arterial and venous samples of blood were drawn one-half hour after the onset of the paroxysm of tachycardia, while the patient was still in the attack. A second venous specimen was drawn one hour after the end of the paroxysm. After leaving the hospital the patient returned for frequent observation. Blood samples were taken after the patient was put to bed at absolute rest for one-half hour, the

*From the Physiological Division of the Medical Clinic of the Johns Hopkins University and Hospital.
†Working under the tenure of the William Bingham Fellowship in Medicine.

1. Stewart, H. J.: To be published.
2. Barcroft, J.; Bock, A. V., and Roughton, F. J.: Heart **9**:7, 1921.
3. Meakins, J.: Heart **9**:185, 1922.

time being arranged so that it was at least two hours after the previous meal. The blood was drawn without stasis under albolene as described by Stadie [4] for arterial blood and by Lundsgaard [5] for venous blood. The blood samples were at once analyzed in duplicate, using the "giant" Van Slyke apparatus and the combined method of Van Slyke and

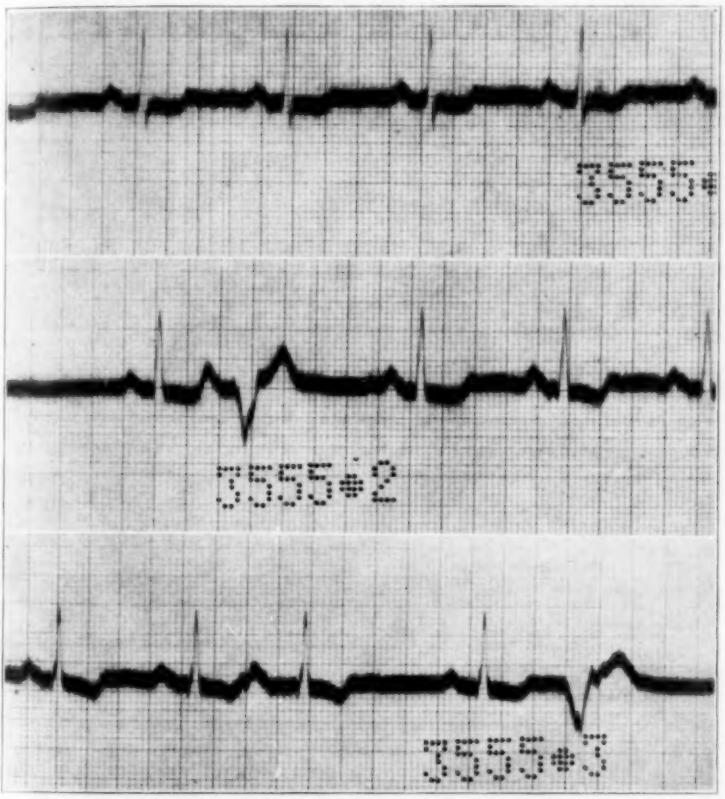

Fig. 1.—Film shows numerous auricular and right and left ventricular extrasystoles. This interpretation, as well as the interpretation of the succeeding films, was made from a long tracing, which it was not possible to reproduce in full. Taken Jan. 27, 1922, soon after admission.

Stadie [6] for determining the oxygen and carbon dioxid on the same sample of blood. The vital capacity was calculated from West's [7]

4. Stadie, W. C.: J. Exper. Med. **30**:215, 1919.
5. Lundsgaard, C.: J. Biol. Chem. **33**:133, 1918.
6. Van Slyke, D. D., and Stadie, W. C.: J. Biol. Chem. **49**:1, 1921.
7. West, H. P.: Arch. Int. Med. **25**:306 (March) 1920.

formula based on the body surface area, which was estimated from the height-weight chart of Du Bois and Du Bois.[8]

REPORT OF CASE

E. G., female, colored, aged 35, admitted Jan. 26, 1922, and discharged March 10, 1922.

Diagnosis.—Chronic rheumatic endocarditis; chronic myocarditis; mitral insufficiency; auricular and ventricular extrasystoles; auricular paroxysmal tachycardia; myocardial insufficiency; chronic tonsillitis.

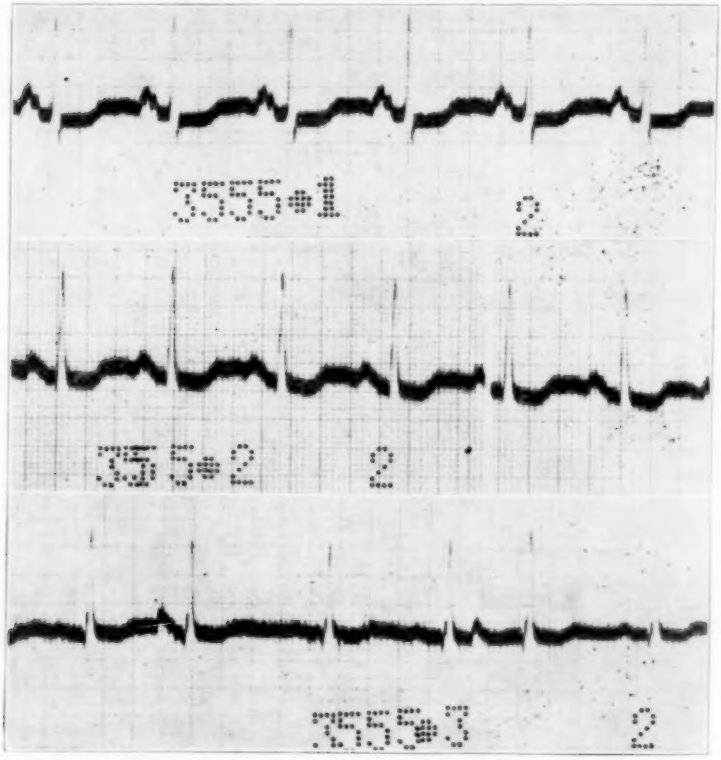

Fig. 2.—Only occasional auricular extrasystoles. Taken after patient had been receiving quinidin sulphate for two days (Feb. 7, 1922).

Complaint.—Attacks of palpitation, difficulty in breathing and swollen legs.

Past History.—Acute rheumatic fever every summer from the age of 9 years up to 10 or 12 years ago. Pneumonia at 17, followed by cardiac failure of 26 months' duration. Pneumonia again four years ago at which time she was in bed for four weeks. A third attack of pneumonia two years ago. Frequent attacks of tonsillitis from childhood until ten years ago. She has always been

8. Du Bois, D., and Du Bois, E. F.: Arch. Int. Med. **17**:863 (June) 1916

short of breath as far back as she can remember, but this has been accentuated in the last seven years. Since then even talking will bring on dyspnea.

Present Illness.—Began in February, 1921, with palpitation, dyspnea and swelling of the abdomen. The patient had a choking sensation, and numbness in the arms and legs. She was in bed for four weeks, and for two months after this she could only walk a few steps. After this she did light work until Thanksgiving, 1921, at which time she had an attack similar to the one in February. Since then she has had frequent attacks of palpitation, described as a "pumping of the heart," and as leaving her chest sore. Attacks are often

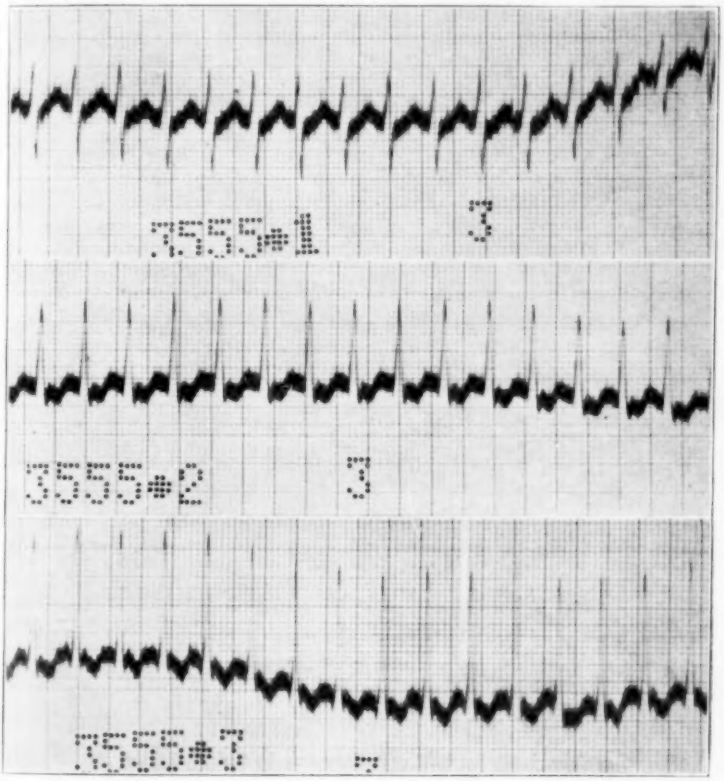

Fig. 3.—Taken during attack of Feb. 23, 1922. Auricular paroxysmal tachycardia, rate 198.

preceded by blackness before the eyes. She has had frequent attacks of vomiting, with no relation to meals. Edema has been present since last Thanksgiving.

Physical Examination.—Temperature, 98.8 F.; pulse, 80; respiration, 20. Slightly obese. No general glandular enlargement. Perforated nasal septum. Teeth poorly kept, snags, several missing, some dentistry. Tonsils large, ragged and cryptic. Lungs clear except for a few fine râles at both bases posteriorly. There is a systolic heave of the precordium. No shock, no thrill. The relative cardiac dulness extended 13 cm. to the left in the fifth interspace and 4.5 cm.

to the right in the fourth intercostal space. Cardiac rhythm regular except for numerous extrasystoles. There is a prolonged rough systolic murmur over the apex, well transmitted to the axilla and to the base. Second pulmonic sound accentuated. Blood pressure was 110/75. Liver edge just below umbilicus. Liver tender. Slight edema of ankles.

Laboratory Findings.—Blood examination negative. Vital capacity 33 per cent. normal. Phenolsulphonephthalein, 50 per cent. in two hours. The electrocardiogram showed a normal sinus mechanism, numerous auricular and right ventricular extrasystoles (Fig. 1). Blood chemistry normal. Blood Wassermann negative. Urine normal.

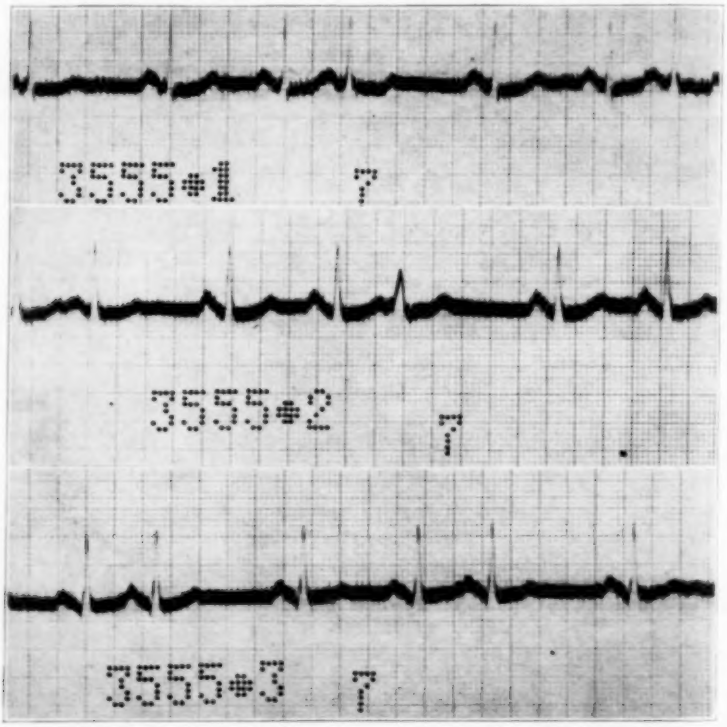

Fig. 4.—Taken June 16, 1922. Patient has had no quinidin sulphate since leaving the hospital. Numerous auricular and occasional right ventricular extrasystoles.

Course and Treatment.—The patient was put to bed on admission. Feb. 6, 1922, quinidin sulphate therapy was started and February 10, after 27 gm. of the drug, the auricular ectopic beats had almost entirely disappeared (Fig. 2). February 12, after 2 gm. more of quinidin, there were no ectopic beats and the drug was discontinued. Although the patient was up several hours each day, no ectopic beats were noted for more than a week, in spite of discontinuance of quinidin sulphate. Her vital capacity rose to 61 per cent. of normal. February 21, there was a rise in temperature to 102.6 F. and on the next day the patient's tonsils were injected, the tonsillar glands swollen and tender. The

temperature remained elevated for a week. At midnight of February 23, the patient was suddenly seized with dyspnea and palpitation. She became nauseated and vomited. The cardiac rate was 200 on auscultation. This attack lasted for one hour. An electro-cardiogram showed auricular paroxysmal tachycardia (Fig. 3). The following day there were occasional extrasystoles. A throat culture showed *Streptococcus hemolyticus*. February 25, the patient had two paroxysms of tachycardia during the course of the morning, with a cardiac rate of 215. Each paroxysm lasted one hour. Electrocardiograms taken February 25 during these attacks were not suitable for publication, but a similar record taken February 23 is published instead (Fig. 3).

Blood samples were taken about one half hour after the onset of the second paroxysm February 25. At this time the cardiac rate was 215 and respiration 40; patient was vomiting, veins were distended and there was cyanosis of lips, fingers and ear lobes. No signs of pulmonary congestion. The arterial blood was 85.3 per cent. saturated with oxygen and the venous blood 16.7 per cent. saturated; coefficient of utilization of the oxygen carrying power, 68.6 per cent.; oxygen capacity, 21.14 volumes per cent.; arterial carbon dioxid content, 28.07 volumes per cent. and venous carbon dioxid content, 46.69 volumes per cent.; respiratory quotient, 1.290. One hour after the attack ceased, the venous blood was 68.1 per cent. saturated; oxygen capacity, 19.62 volumes per cent.; venous carbon dioxid content, 44.51 volumes per cent. Pulse, 80; respiration, 32. Vital capacity, 39 per cent. of normal. The patient was comfortable, there was no cyanosis, no signs of pulmonary congestion, and vomiting had stopped. She felt so worn out that she asked to have the arterial puncture delayed.

Between February 25 and March 2, 1922, the patient received 6.0 gm. of quinidin sulphate, during which time there was no further attack and the patient steadily improved. March 5, her vital capacity had risen to 68 per cent. normal. Tonsillectomy was advised but the patient refused operation. The patient was discharged in fairly good condition. The patient was seen at frequent intervals after discharge. April 7, 1922, when her heart was slow and regular, her venous blood was 47.7 per cent. saturated with oxygen, the oxygen capacity being 18.76 volumes per cent.; carbon dioxid content, 55.91 volumes per cent.; vital capacity 61 per cent. normal. She had had several brief attacks of palpitation since her discharge, but was able to carry on her work. June 16, 1922, when the cardiac mechanism was still normal, her arterial blood was 100 per cent. saturated, venous blood 45.8 per cent. saturated with oxygen; coefficient of utilization, 44.2 per cent.; oxygen capacity, 15.81 volumes per cent.; arterial carbon dioxid content, 42.35 volumes per cent; venous carbon dioxid, 50.50 volumes per cent.; respiratory quotient, 0.871. Pulse, 65; respiration, 22; vital capacity 64 per cent. normal. No cyanosis, no edema. Slight dyspnea on exertion. Electrocardiogram showed numerous auricular and occasional right ventricular extrasystoles, normal sinus mechanism (Fig. 4).

DISCUSSION

This case is interesting not only on account of the studies of the blood gases, but also on account of the connection between infection and disturbance of the cardiac mechanism. With normal sinus mechanism the arterial blood was completely saturated with oxygen while the venous blood showed an abnormally low saturation, the coefficient of utilization being 44.2 per cent. (the normal range of which is from 20 to 30 per cent.). These findings point to an impairment of the peripheral circulation even with a regular cardiac rhythm, or, in other words, to a stagnant or ischemic anoxemia (Barcroft[9]). During the

9. Barcroft, J.: Lancet **1**:487, 1920.

attack of tachycardia there was an anoxic anoxemia and a greatly increased ischemic anoxemia, as shown by the fall in arterial oxygen saturation and the much lower venous content of oxygen, the coefficient of utilization being 68.6 per cent. There were no signs of pulmonary congestion to account for the anoxic anoxemia, and the only cause which suggests itself for the incomplete oxygenation of the blood in the lungs is the reduction in circulatory minute volume brought about by the tachycardia through a greatly decreased output per beat. Barcroft,

TABLE 1.—OBSERVATIONS ON THE BLOOD GASES.

		Oxygen Content		Oxygen Saturation			Oxygen Consumption	Oxygen Capacity		Carbon Dioxid Content		Difference in Carbon Dioxid	
Date	Mechanism	Arterial Vol. %	Venous Vol. %	Arterial %	Venous %	Coefficient of Utilization	Vol. %	Vol. %	Hemoglobin %	Arterial Vol. %	Venous Vol. %	Vol. %	Respiratory Quotient
2/25/22 In attack	Paroxysmal tachycardia	18.06	3.52	85.3	16.7	68.6	14.51	21.14	114.3	28.07	46.09	18.02	1.290
2/25/22 1 hour after end of attack	Normal mechanism	.....	13.26	.....	68.1	.....	.....	19.62	106.1	.....	44.51	.....	.....
4/ 7/22	Normal mechanism	.....	8.94	.....	47.7	.....	.....	18.76	101.4	.....	55.91	.....	.....
6/16/22	Normal mechanism	16.08	7.24	100.0*	45.8	44.2	8.84	15.81	85.5	42.35	50.05	7.70	0.871

* Difference between arterial oxygen content and oxygen capacity is within experimental error.

TABLE—2.—CLINICAL OBSERVATIONS

	Pulse		Respiration					
Date	Arterial Puncture	Venous Puncture	Arterial Puncture	Venous Puncture	Blood Pressure	Artery Used	Vital Capacity, per Cent. Normal	Remarks
2/25/22 In attack	215	215	38	40	.....	Right radial	..	Marked cyanosis; veins engorged; vomiting; no râles at lung bases
2/25/22 1 hour after	...	80	..	32	.....	.....	20	Patient comfortable; no cyanosis
4/ 7/22	...	92	..	30	125/90	.....	61	No cyanosis, no edema; dyspnea on exertion; no râles
6/16/22	60	68	20	24	105/85	Right radial	64	No cyanosis, no edema; dyspnea on exertion; no râles

Bock and Roughton found an arterial oxygen saturation of 96.8 per cent. during an attack of paroxysmal tachycardia. They concluded from this that there was no decrease in the arterial saturation but rather an increased saturation during tachycardia. The arterial oxygen saturation was not determined in the presence of the normal sinus rhythm and this conclusion is based on the assumption that the arterial saturation was normally 95 per cent. It is possible, however, that the arterial saturation normally may have been higher than 96.8 per cent., so that there may have been a slight decrease in the saturation. The anoxic anoxemia found in this case is also contrary to the conclusion

of Meakins that tachycardia without pulmonary congestion and edema does not produce a decrease in the oxygen saturation of the arterial blood. In a footnote to Table 2, Meakins [3] states that the "samples were taken from fifteen to twenty minutes after the end of the tachycardia in each instance." Under these circumstances, the oxygen saturation could have returned to normal in the interval between the end of the tachycardia and the taking of the sample. It hardly seems justifiable to draw such a sweeping conclusion from the figures reported in this table. The rapid return of the circulation to a relatively normal status is shown by the fact that the venous oxygen content was normal one hour after the end of the paroxysm.

The extremely low arterial carbon dioxid content during the attack was probably due to overventilation of the lungs and to slowing of the circulation so that the blood remained in the lung capillaries longer than normally. The p_H of the arterial blood would be interesting.

During the attack of tachycardia the oxygen capacity of the patient's blood corresponded to a hemoglobin of 114.3 per cent. One hour later this was 106.1 per cent. and on subsequent occasions was found to have fallen to 101.4 per cent. (April 7) and 85.5 per cent. (June 16). This change may indicate that the patient responded to an increased demand for oxygen as a result of the series of attacks by a physiologic increase in the amount of circulating hemoglobin.

The patient was too ill to take a vital capacity test during the paroxysm, but one-half hour after the attack it was 39 per cent. normal, while with a regular heart action it ranged from 64 to 68 per cent. normal.

SUMMARY

A case of auricular paroxysmal tachycardia was studied from the point of view of the blood gases. The findings include:

1. Marked decrease of the arterial oxygen saturation without demonstrable pulmonary congestion to account for this.

2. Extremely low carbon dioxid content of the arterial blood during the paroxysm.

3. Very low oxygen saturation of the venous blood, part of which was attributable to the anoxic anoxemia, but the greater part was a true stagnant anoxemia due to slowing of the circulation. This stagnant anoxemia had entirely disappeared one hour after the end of the attack.

4. Greatly increased coefficient of utilization during the paroxysm, indicating a very slow circulation rate.

5. Decrease in vital capacity immediately following the paroxysm.

In addition, there appeared to be a close connection between an acute infection and the disturbance of the cardiac mechanism. It was also noted that during quinidin sulphate therapy ectopic beats which had been numerous and troublesome disappeared.

OBSERVATIONS OF THE CARDIOVASCULAR SYSTEM IN THYROID DISEASE*

W. J. KERR, M.D., AND GEORGE C. HENSEL, M.D.
SAN FRANCISCO

The importance of the cardiovascular signs and symptoms in thyroid disease has been known from the earliest writings on goiter. Parry,[1] in 1786, recognized the seriousness of these manifestations, his first case presenting grave cardiac disorders resulting in death. Since that time practically all authors have agreed that the outcome of any case is greatly influenced by the state of the circulation and its response to therapy. Möbius,[2] in 1896, emphasized the importance of tachycardia, palpitation, forceful beating of the heart and arrhythmia in the syndrome of thyrotoxicosis, and stated that exophthalmic goiter patients suffer and die mainly because of cardiac changes. Hirschfelder[3] reviewed the subject and gave the prevailing opinions regarding the cardiovascular findings and their treatment. Forchheimer[4] directed therapeutic measures in thyroid disease toward the support of the circulation. Kocher[5] and others believed that the surgeon should be guided by the cardiac condition in choosing the time and extent of operation.

In a careful electrocardiographic study of fifty-one goiter patients, Krumbhaar[6] recorded the findings before and after surgical treatment. His observations indicated that the effects of prolonged thyroid intoxication on the heart were progressive in nature. Such patients developed high pulse pressure, hypertrophy, arrhythmias, heart block and changes in the *T*-wave. It is also of interest to note that in his cases successful medical or surgical treatment resulted in the disappearance of some of these abnormal manifestations. In one of his cases transient auricular fibrillation occurred. Fahrenkamp[7] reports a case of thyrotoxicosis with paroxysms of auricular fibrillation of short duration, and auricular

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* From the Medical Division, University of California Hospital.
* Read before the California State Medical Society, Yosemite Valley, May, 1922.

1. Parry: Collections from the Unpublished Writings of the late C. H. Parry, Underwood, London, 1825.
2. Möbius: Die Basedowsche Krankheit, Nothnagel's System, **22**:1, 1896.
3. Hirschfelder, A. D.: Diseases of the Heart and Aorta, Philadelphia, J. B. Lippincott Co., 1910, pp. 574-592.
4. Forchheimer, F.: The Prophylaxis and Treatment of Internal Diseases, New York, D. Appleton & Co., 1910, pp. 465-468.
5. Kocher, quoted by Hirschfelder, footnote 3.
6. Krumbhaar, E. B.: Electrocardiographic Observations in Toxic Goiter, Am. J. Med. Sc. **155**:175-203, 1918.
7. Fahrenkamp, K.: Vorübergehende komplete Herzunregelmässigkeiten unter dem Klinischen Bilde der Arhythmia perpetua, Deutsch. Arch. f. klin. Med. **117**:1-12, 1914.

fibrillation has frequently been observed as a permanent condition in the later stages of the disease. Auricular flutter, paroxysmal tachycardia, extrasystoles and sinus arrhythmia have also been noted. Blackford and Willius [8] found auricular flutter associated with exophthalmic goiter in three out of a series of sixteen cases of auricular flutter. White and Aub,[9] in a careful electrocardiographic study, found auricular fibrillation in six out of forty-seven cases of hyperthyroidism. Three of these were of the paroxysmal type. Paroxysmal flutter occurred in one case. Goodpasture [10] has described an unusual type of myocardial regeneration in hyperthyroidism.

The syndrome known as "neurocirculatory asthenia" or "effort syndrome" has been confused with thyrotoxicosis. It has been shown by Addis and Kerr [11] and others [12] that this syndrome is as frequent in persons without any thyroid enlargement as in those with moderate or great enlargement.

The purpose of this paper is to report the cardiovascular condition of patients with thyroid disease entering the University of California Hospital for treatment during the past two years. In addition to the usual observations on the size of the heart, condition of the vascular system, pulse rate, blood pressure, pulse pressure and metabolic rates, a special effort has been made to study the types of irregularity revealed by means of electrocardiograms and polygraph tracings.

GENERAL CONSIDERATIONS

Of the 181 goiters studied, 123 were classified as adenomas and fifty-eight as hyperplasias. In reviewing the adenomas no attempt has been made to draw a sharp distinction between the toxic and nontoxic types. Approximately, half of these cases showed no signs of toxicity, and in a relatively small number the goiter produced pressure symptoms only. The average age of these patients was 46 years and a tumor was noted at the average age of 29 years, or seventeen years before appearing for treatment. Symptoms had been present on the average for eight and three tenths years. Females were affected 106 times and

8. Blackford, J. M., and Willius, F. A.: Auricular Flutter, Arch. Int. Med. **21**:147-165 (Jan.) 1918.

9. White, P. D., and Aub, J. C.: The Electrocardiogram in Thyroid Disease, Arch. Int. Med. **22**:766-769 (Dec.) 1918.

10. Goodpasture, E. W.: Myocardial Necrosis in Hyperthyroidism, J. A. M. A. **76**:1545 (June 4) 1921.

11. Addis, T., and Kerr, W. J.: The Relative Frequency in Recruits with and Without Thyroid Enlargement of Certain Signs and Symptoms Which Occur in Neurocirculatory Asthenia, Arch. Int. Med. **23**:316-333 (March) 1919.

12. Norris, G. W., and Landis, H. R. M.: Diseases of the Chest and the Principles of Physical Diagnosis, Philadelphia, W. B. Saunders Company, 1920, pp. 692-695.

males seventeen times. Cardiovascular symptoms were more or less marked in 44 per cent. of the cases. Rapid and forceful beating of the heart and "palpitation" were the symptoms usually complained of, although vasomotor disturbances, irregularities of the heart, dyspnea and breathlessness were frequently noted. Pain in the region of the heart and anginal attacks were rare. Central nervous system symptoms, including nervousness, tremors, astasia abasia and emotional instability, were described in fifty-eight cases. Gastro-intestinal symptoms, usually diarrhea, or diarrhea alternating with constipation, were complained of in only four cases. There was marked progressive loss of weight in

TABLE 1.—GENERAL FINDINGS

Type of Goiter	No. of Cases	Sex	Average Age, Years	Average Age Tumor Noted	Average Duration of Symptoms	Number with Eye Signs	Number with C. N. S. Symptoms	Number with Gastro-Intestinal Symptoms	Marked Loss of Weight	Average Basal Metabolism, per Cent.	Number of Deaths
Adenomas toxic and nontoxic	123	M. 17 F. 106	41.38	29.2 years	8.3 years	1 slight 6 doubtful	58	4	8	30.2 + (all forms) 47 + (toxic only)	2
Hyperplasias	58	M. 15 F. 43	36.4	33.9 years	3 months	44 5 doubtful	56	17	38	58.7 +	7

TABLE 2.—GENERAL CARDIOVASCULAR FINDINGS

Type of Goiter	No. of Cases	Cardiac Symptoms	Per Cent. with Cardiac Symptoms	Average Pulse Rate	Average Blood Pressure		Average Pulse Pressure	Number with Cardiac Enlargement	Number with Murmurs	Number with Bruit Over Thyroid or Temporal Arteries	Number with Signs of Decompensation
					Systolic	Diastolic					
Adenomas toxic and nontoxic	123	54	44	85 (95 in toxic cases)	133	78	55	41	43	3	3
Hyperplasias	58	53	91	107	141	71	70	43	46	33	15*

* Three of these cases presented unusual and marked systolic pulsations of the veins of the forearms and hands.

eight cases and a gain in two cases. In no case was there marked exophthalmos. When the eye changes were noted, usually only one or two of the minor signs were described. The average basal metabolic rate, when determined, was 30.2 per cent. above the theoretic normal, but when the nontoxic cases were excluded, the average rate was 47 per cent. above the theoretic normal. There were two deaths.

Of the fifty-eight cases with hyperplasia, forty-four presented exophthalmos and other eye signs, and in five others these eye signs were slight or doubtful. The average age was 36.4 years and the tumor was observed at the average age of 33.9 years, or two and five-tenths years before entering the hospital for treatment. Females were affected forty-three times and males fifteen times. Symptoms had been present

for a relatively brief period. In about one-third of the cases the tumor was noticed before the onset of symptoms; in about one-third, the appearance of the symptoms preceded the discovery of the tumor; and in the remainder, the symptoms and tumor appeared at the same time. The average duration of symptoms was about three months. Cardiovascular symptoms were complained of in 91 per cent. of the cases. "Palpitation" and rapid, forceful beating of the heart were usually present; irregularities, dyspnea, breathlessness and vasomotor disturbances were common. Fifteen cases presented signs of decompensation. Central nervous system symptoms were present in fifty-six cases and were more pronounced than with the adenomas. Gastro-intestinal symptoms such as diarrhea and vomiting were complained of in seventeen cases. There was a definite loss of weight in thirty-eight cases. The basal metabolic rate averaged 58.7 per cent. above the theoretic normal. There were seven deaths.

SPECIAL CONSIDERATION OF CARDIOVASCULAR SYSTEM

Symptoms.—A brief statement of the cardiovascular symptoms is given above. It is the prevailing opinion that the hyperplastic goiter causes more profound changes in the circulatory system than is found in association with toxic adenomas. Our observations suggest, however, that, so far as the heart is concerned, the disturbances are practically the same in both groups. Where differences occurred, they seemed to be due mainly to the degree of toxicity. The vascular system, however, showed more pronounced changes in the hyperplastic group than in the group of adenomas. Among the earliest symptoms were tachycardia and a consciousness of the heart beat. Many patients complained of attacks of "palpitation." These spells, which were more frequent later in the disease, probably represent paroxysmal attacks of auricular fibrillation or flutter. Throbbing of the vessels in the neck and periphery, pulsation in the thyroid and a heaving precordium were usually marked in severe cases. Sleep was frequently interfered with because of these sensations and such patients preferred to lie on the right side. Dyspnea and breathlessness on exertion, and in the later stages cough, progressive edema, cyanosis and other signs of decompensation were observed where proper treatment had not been instituted. Goiters producing pressure symptoms were relatively infrequent causes of cardiovascular disturbances, as compared with the overacting glands.

Physical Signs.—Inspection in the early cases revealed very little aside from a forceful apex impulse in the usual position, slightly increased carotid pulsations and flushing of the face and neck. As the disease advanced, the apex impulse became more forceful with a diffuse heaving of the precordium. The apex impulse was then displaced to the

left and, in later stages, downward. The carotid arteries and peripheral vessels showed increased pulsations, and capillary pulsation was frequently noted, especially in the hyperplastic cases. When the myocardium began to fail, the venous pressure rose, the veins stood out and they occasionally showed unusual systolic pulsations extending to the lower arm and hand (noted in three of our cases). When decompensation began, the usual signs appeared: such as pulsating liver, systolic venous pulse in the neck, edema of the lungs and edema of the legs advancing to anasarca. During the stage of decompensation, the heart was frequently irregular and no sign of an *A*-wave could be found in records from the jugular vein.

On palpation the apex impulse was usually forceful and showed no displacement in early cases; but as the condition advanced, the impulse became more marked and diffuse, and it moved to the left and downward. A systolic or presystolic thrill at the apex, or a systolic thrill at the pulmonic area was noted in a few cases. A distinct shock was felt at the pulmonic area, accompanying the second sound. A systolic thrill was frequently felt over the thyroid vessels in hyperplastic glands, rarely in adenomas. The pulse was usually soft and often times dichrotic. A water-hammer pulse was common in the hyperplasias. The rate was quickened in toxic cases, being 93 in the toxic adenomas and 107 in the hyperplasias in our series. In the early stages the pulse was generally regular, although a sinus arrhythmia of the respiratory type was frequently observed. Later, many cases showed the more unusual types of irregularities, and in the terminal stages they were very commonly observed.

By percussion the heart was found to be gradually enlarged to the left and downward; there was a well defined increase in dulness in the third and fourth left interspaces, as is seen in organic mitral disease, and later the dulness was increased to the right. Enlargement, usually to the left, was noted in forty-one adenomas and in forty-three hyperplasias. In the absence of thymic enlargement or a substernal extension of the thyroid, the substernal dulness was found to be increased, due to the dilatation of the great vessels.

Auscultation revealed the signs of an overacting heart in toxic cases. The sounds were quickened, ringing and loud, giving an impression of hurried ineffectiveness. As the condition advanced, a soft systolic murmur was usually heard at the apex and a short, rough, systolic murmur was heard at the pulmonic area. Later a loud systolic murmur was frequently heard all over the precordium and was transmitted to the vessels of the neck, with a bruit over the thyroid vessels and gland. A definite bruit was noted over the gland in thirty-three cases of hyperplastic thyroids and in only three of the cases with adenomas. In the advanced stages of myocardial failure a diastolic

murmur was occasionally heard at the pulmonic area or a soft systolic murmur appeared over the tricuspid area. Murmurs were noted in our series in forty-three cases of adenomas and in forty-six cases of hyperplasia.

An unusually large number of cardiac irregularities were observed. Of sinus arrhythmia we have no accurate data as its finding was considered of little significance. It was frequently observed and possibly should be studied further. Extrasystoles were observed in only nine cases and in two of these it is probable that an unrecognized auricular fibrillation was present. Auricular fibrillation was observed in twenty-nine cases, occurring in nine cases with adenomas and twenty cases with hyperplasia. In fifteen of the twenty-nine cases, the fibrillation was paroxysmal in type and in several cases may attacks were observed. Figure 1 shows the frequency and duration of such attacks in one of our cases. In eight cases auricular fibrillation alternated with auricular flutter, and in two cases auricular flutter was observed alone. Paroxysmal auricular tachycardia with a rate of 190 occurred in one case (Table 3).

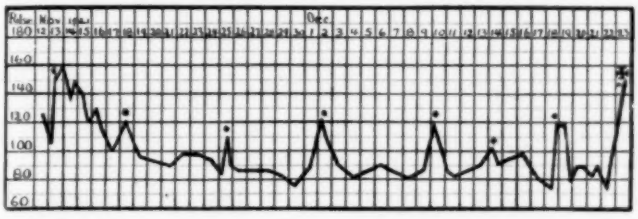

Fig. 1.—Case 9102. Paroxysmal auricular fibrillation. Paroxysms indicated by asterisks. Death occurred one and one-half hours after operation in an attack of auricular fibrillation which began during the operation. All attacks responded to digitalis in moderate doses except the one preceding death.

These observations on the frequency of cardiac irregularities have suggested that many of the attacks of "palpitation" which patients describe are due to the disturbance of the normal mechanism of the heart beat by the inception of one of these unusual rhythms. Such attacks frequently came on suddenly and usually lasted only a short time. They were accompanied by a sense of fulness in the chest, a disagreeable, rapid, forceful action of the heart, flushing of the face and neck, and breathlessness. The termination was usually abrupt. On questioning patients who were seen during attacks of auricular fibrillation or flutter, it was found that their sensations were the same as those experienced during the previous spells of so-called palpitation. In our opinion, this shows pretty clearly that what they call palpitation is really the result of serious auricular fibrillation or flutter. We feel sure that this has not been sufficiently recognized in the past.

Roentgen-ray studies on the toxic cases generally showed the heart to be enlarged to the left with widening in the region of the conus and left auricle—the so-called "mitral type." In some cases, particularly of the hyperplastic group, the heart was of the "aortic type" with the great-vessel shadow definitely increased.

Blood pressure determinations showed in the adenomas an average of 133 mm. mercury (systolic), 78 mm. mercury (diastolic) and a pulse pressure of 55 mm. mercury, while in the hyperplasias the average

TABLE 3.—Cardiac Irregularities

Type of Goiter	No. of Cases	Auricular Fibrillation	Auricular Flutter	Paroxysmal Tachycardia	Extra-systoles	Sinus Arrhythmia
Adenomas toxic and nontoxic	123	9 (4 paroxysmal) (2 alternating with auricular flutter)	3 and 1 probable (2 alternating with auricular fibrillation)	1 (rate 190)	6 including 2 cases of probable auricular fibrillation	Frequent; no exact data
Hyperplasias	58	20 (11 paroxysmal) (6 alternating with auricular flutter)	4 and 2 probable (all alternating with auricular fibrillation)	0	3	Frequent; no exact data
Totals	181	29	7 3 probable	1	7 2 doubtful	Frequent

TABLE 4.—Blood Pressure in Toxic Adenomas

Case Number	Before Operation	After Operation
11447	215/105	140/80 6 mos. later, 170/90
12349	190/100	140/70
12778	160/80	128/75
13489	150/80	124/60
11755	188/100	133/70
13828	190/95	130/70
13451	180/110	145/90
8541	190/100	160/80
10757	238/142	160/100

TABLE 5.—Blood Pressure in the Hyperplasias

Case Number	Before Operation	After Operation
12976	152/86	122/82
11586	145/65	138/45
10444	140/90	128/75

was 141 mm. mercury (systolic) and 71 mm. mercury (diastolic) with a pulse pressure of 70 mm. mercury. In several cases in which the systolic and diastolic pressures were high before operation, a marked fall was observed following surgical treatment. Some of the more striking examples are shown in Tables 4 and 5. In one patient with a hyperplastic goiter who had a blood pressure of 200/100 on admission, there was a fall to 178/65 after medical treatment.

Venous Pressures and Pulsations.—No attempt was made to measure accurately the venous pressures, but in advanced cases the pressure in

the veins was definitely increased. In three cases we observed pulsating peripheral veins in the arms and hands, which cleared up after treatment.

Electrocardiographic and *polygraphic* tracings were made in most of the cases showing unusual irregularities and in some of the uncomplicated cases. Twenty-five cases were studied at intervals while in the hospital. In addition to the changes in rhythm noted, there were certain variations in the auricular complex which were frequently observed in more severe cases. The *P*-waves were widened and increased in amplitude, frequently slightly notched in Lead I and having a diphasic character in Lead III. These features were noted in ten out of fourteen cases with regular rhythm. The *P-R* interval was five

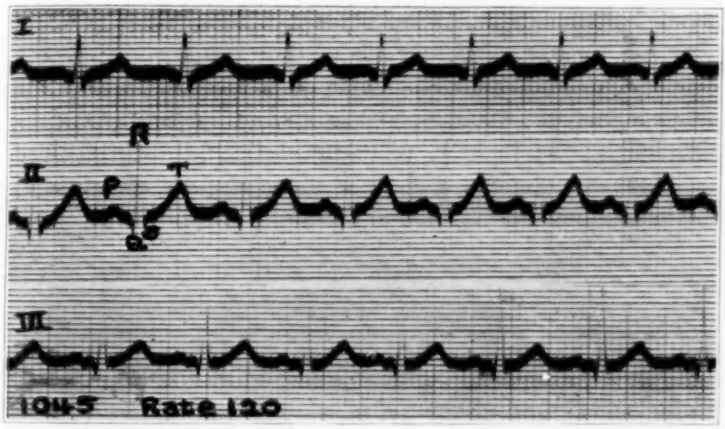

Fig. 2.—Electrocardiogram 1045. Marked hyperplasia. Rate 120. Notching of "P" waves in Lead III. Prominent "T" waves, all leads. Died after operation of marked-thyrotoxicosis and focal necrosis of liver and pancreas. (For this and all succeeding electrocardiograms, the time marker records twenty-fifths of a second. The galvanometer string is so standardized that deflections of one centimeter represent one millivolt.)

twenty-fifths second in three cases and there was an arborization block in one case. Bundle branch lesions were not observed. Right hypertrophy was shown in two cases and left hypertrophy in three cases. The *T*-wave, when flattened or inverted in Leads I and II, has been found to indicate a bad prognosis in accordance with the findings of Krumbhaar. In our series there were six such cases, all showing advanced myocardial disease and, as was to be expected, two, or 33 per cent., of the patients died. Examples of the various types of irregularities are shown in Figures 2 to 5.

Diagnosis.—The diagnosis of the types of goiter studied were made on the clinical signs and symptoms combined with pathologic findings at operation and necropsy. The cardiac symptoms and signs were usually obvious, although careful observation and instrumental means were frequently necessary to differentiate the irregularities encountered.

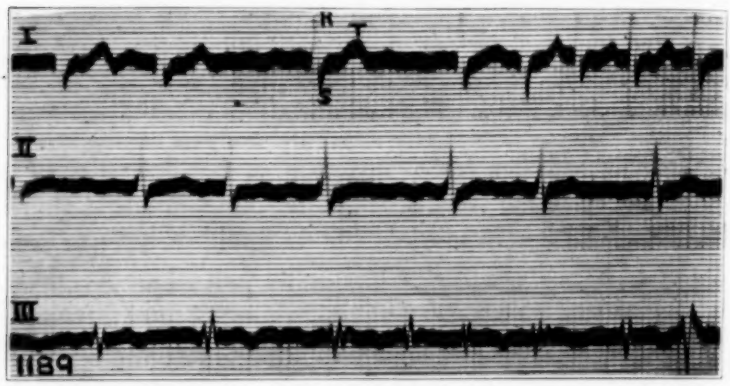

Fig. 3.—Electrocardiogram 1189. Marked hyperplasia. Paroxysmal auricular fibrillation. Slight right hypertrophy. Inverted "T" waves in Lead III.

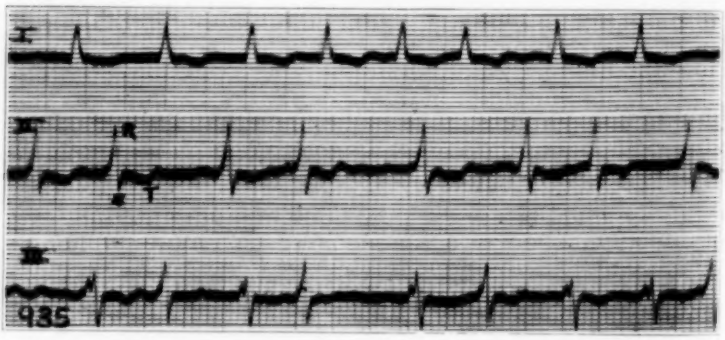

Fig. 4.—Electrocardiogram 935. Marked hyperplasia. Advanced myocardial changes with decompensation, peripheral venous pulsations. Auricular fibrillation. Inverted "T" waves in all leads. "Q-S" interval two twenty-fifths of a second. Radium treatment. Living after six months.

Treatment.—No preliminary treatment was given in the nontoxic or moderately toxic adenomas previous to operation. The patients with more advanced toxic adenomas, with signs of cardiac failure, and most of the patients with hyperplasias were given preliminary medical treatment or received medical treatment alone. Mental and physical

rest was insisted on. Bromids or quinin hydrobromate were given when indicated. Ice bags were used over the thyroid gland and heart in the more toxic cases with considerable relief from distressing symptoms. Digitalis, in the form of the tincture, was used, when indicated, under careful supervision. In moderate doses the drug produced excellent results and was very useful in controlling and, possibly, in preventing attacks of abnormal cardiac rhythms, particularly auricular fibrillation. One patient died during operation, from the effects of toxic procain used as a local anesthetic. Another death occurred from auricular fibrillation with marked signs of thyrotoxicosis developing two days after operation. Quinidin sulphate seemed to have a beneficial effect in controlling attacks of auricular fibrillation in one case, although of no benefit in several others. Cardiac decompensa-

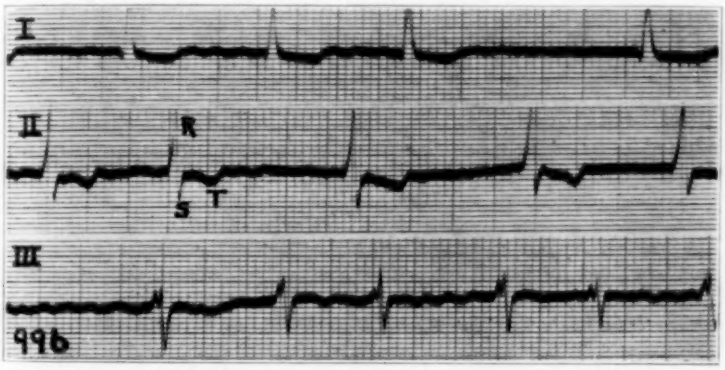

Fig. 5.—Electrocardiogram 996. Same as 935 after digitalis therapy. Rate reduced from 135 to 75 per minute.

tion was treated by the approved methods, although excessive purgation was very exhausting in some cases. Roentgen-ray treatment was used in many cases of hyperplasia before operation and in a few cases it was the only local treatment employed. Radium emanations in bare tubes of from 6 to 10 mc. were inserted into some of the more serious hyperplastic goiters with marked improvement. (These cases are being reported elsewhere by Dr. W. I. Terry.) Various methods of surgical treatment were employed, including ligation, enucleation of adenoma, partial lobectomy, bilateral subtotal lobectomy, etc.

One of the most striking observations made in this series of cases has been the degree of cardiac relief noted by the patient after removal of an overacting thyroid gland.

Prognosis.—In our series it has been demonstrated that the condition of the heart generally determined the outcome of the case. Deaths

from other causes, except marked increase of toxicity following operation in severe cases, were rare. Electrocardiographic demonstration of flattened or inverted *T*-waves in Leads I and II have indicated an unfavorable outcome. Heart block and disorders of the cardiac rhythm have been noted in the more severe cases. Signs of decompensation and advancing edema have indicated prolonged medical treatment or radiotherapy. Embolism and coronary disease were rare. Focal necroses of the liver and pancreas followed operation in one case and caused the death of the patient.

Mortality.—In our series there were nine deaths, seven occurring in cases with hyperplasia, one with a mixed gland and one with an adenoma of the plunging type. The findings in these cases have been briefly summarized below.

REPORT OF CASES

Case 1 (8505).—Female, aged 46. Symptoms and tumor for eight years with slight pressure on trachea; enlarged heart; blowing systolic murmur at mitral and pulmonic areas; loud bruit and thrill over gland; pulse, 130; blood pressure 120/80 mm. mercury, basal metabolism 70 per cent. plus. She was given preliminary medical treatment, and radium, 10 mc., was inserted into the gland with slight improvement. Later bilateral subtotal lobectomy was done with only slight improvement. One month after operation she had a brief attack of auricular fibrillation. Basal metabolism, 66 per cent plus. Four months after operation basal metabolism was 58 per cent. plus. Then nine exposures to the roentgen-ray in another city were followed by marked thyrotoxicosis, pulse 200, coma, delirium and death. At the necropsy a large amount of hyperplastic gland was found surrounding the trachea and extending beneath the manubrium.

Diagnosis.—Recurrent hyperplasia with marked thyrotoxicosis.

Case 2 (12563 and 13060).—Male, aged 39. Symptoms present three years; very marked during past five months; tumor noted three weeks; heart enlarged; pulse, 120; blood pressure, 120/64; slight eye signs; marked bruit; basal metabolism, 79 per cent. He was given medical treatment and radium 6.5 mc., was inserted into the gland. Very slight improvement. Two months later, a bilateral partial lobectomy was done. Thirteen days after operation there developed progressive jaundice, coma, convulsions, dyspnea and cyanosis. Urobilin was present in the urine (no leucin or tyrosin) and the man died in coma. The necropsy showed marked acute focal degeneration of the liver; focal necrosis of pancreas; hyperplasia of thymus.

Diagnosis.—Hyperplasia with marked thyrotoxicosis and liver degeneration.

Case 3 (13360).—Female, aged 31. Tumor present five years; symptoms manifested two years with palpitation and diarrhea, heart slightly enlarged with systolic murmur at mitral area and diastolic murmur at pulmonic area. She entered the hospital with a pulse of 180; blood pressure, 160/90; gangrene of right arm. Amputation. Pulse rose to 200; temperature increased from 38 to 42 C., and the patient died with cardiac failure and toxemia. The necropsy showed thrombosis of right subclavian artery. No thrombi found in heart. Right ventricle dilated.

Diagnosis.—Hyperplasia with cardiac dilatation and arterial thrombosis.

Case 4 (10751).—Female, aged 39. Symptoms present for many years; tumor noted for eighteen months, with decompensation for eighteen months with anasarca, marked hypertrophy and dilatation of heart, systolic murmurs at mitral and pulmonic areas, auriculoventricular block (partial), pulse 90, blood pressure 140/60, marked eye signs, basal metabolism, 56 per cent. plus. She

had had six roentgen-ray treatments fifteen months previously. She was given medical treatment, and radium, 7.6 mc., was inserted into the gland, followed by three roentgen-ray treatments. Patient died three months later of decompensated heart. Necropsy (limited to abdominal organs) showed cirrhosis of liver, diffuse brown atrophy, infarct in right kidney.

Diagnosis.—Hyperplasia with advanced myocardial disease and cirrhosis of liver.

Case 5 (8027).—Female, aged 30. Symptoms and tumor present fifteen months; heart enlarged; loud systolic murmur all over precordium; pulse, 130; blood pressure, 140/70; marked bruit over gland; marked eye signs. Preliminary medical treatment with extraction of abscessed teeth and tonsillectomy with slight improvement. Operation: Bilateral partial lobectomy. Patient died during operation from probable effects of toxic procain. She had been given 18 c.c. of tincture of digitalis during the four days previous to operation.

Diagnosis.—Hyperplasia. Anesthetic death.

Case 6 (7630).—Female, aged 35. Extreme symptoms present for eight months with attacks of palpitation resembling auricular fibrillation; tumor noted eight months; heart enlarged; pulse, 108; blood pressure, 135/70; marked eye signs. Radium, 10 mc., was inserted into gland. One month later patient was improved and a bilateral partial lobectomy was done. Pulse was irregular, with auricular fibrillation before operation, and patient received 20 c.c. tincture of digitalis during four days previous to operation. Digitalis was stopped after operation. Two days later fibrillation returned with marked thyrotoxicosis, the patient rapidly failed and died. Digitalis probably should have been continued after operation.

Diagnosis.—Hyperplasia with myocardial changes and paroxysmal auricular fibrillation.

Case 7 (9120).—Female, aged 52. Tumor noted fifteen years; symptoms manifested only three weeks, with marked palpitation in paroxysms, and dyspnea. There had been pressure symptoms for three years. Heart was markedly enlarged, with heaving precordium; pulse, 120; systolic blood pressure, 150; diastolic sound heard to zero; marked capillary pulse; marked bruit and eye signs. Seven paroxysms of auricular fibrillation of brief duration were observed before operation. There were attacks of anginal pain. Preliminary intermittent digitalis therapy was given. The goiter was "stolen." Auricular fibrillation returned during operation and continued until death an hour and a half after operation (Fig. 1). Pathologic section of gland showed colloid goiter with evidence of some hyperplasia. Adenomas also present.

Diagnosis.—Mixed type of goiter with marked myocardial changes and paroxysmal auricular fibrillation. Angina pectoris.

Case 8 (5486).—Female, aged 41. Tumor noted twenty-six years; previous operation thirteen years ago. Tumor returned six years ago, general symptoms manifested five years with pressure symptoms. Heart enlarged; arch widened with probable substernal thyroid; systolic murmur over base transmitted to carotids, and thyroid arteries. Many paroxysms of auricular fibrillation alternating with auricular flutter, flattened *T*-waves in Lead I by electrocardiograph. Pulse 100; blood pressure, 130/60 (variable); no eye signs; marked loss of weight; diarrhea; basal metabolism, 76 per cent. plus. Preliminary medical treatment and six roentgen-ray treatments were given. Patient died two hours after operation with auricular fibrillation. Sections of the gland showed multiple adenomas with hyperplastic and degenerative changes. The sections also suggested the presence of tuberculosis, although no signs of that disease were found elsewhere.

Diagnosis.—Mixed type of goiter with advanced myocardial disease, auricular fibrillation and flutter.

Case 9 (13038).—Male, aged 76. Slight symptoms noted for three years with recent severe pressure symptoms. Tumor noted one and one-half years.

Heart enlarged to left; no murmurs; pulse, 100; blood pressure, 135/75. Plunging type of goiter. Operation difficult. Patient died one and one-half hours after operation from local hemorrhage and pressure on the trachea.

Diagnosis.—Toxic degenerating adenomas with pressure symptoms. Postoperative hemorrhage with tracheal pressure.

CONCLUSIONS

1. The cardiovascular changes in thyroid disease are progressive, and in the most severe cases dominate the clinical picture.

2. The cardiac signs and symptoms in toxic adenomas and hyperplasias differ only with the degree of toxicity. The vascular changes are more marked in the cases of hyperplastic goiter.

3. Cardiac irregularities are more common than is generally recognized. Auricular fibrillation or auricular flutter, usually paroxysmal in type, occurred in about one-third of all toxic cases. We believe that such paroxysmal attacks explain the periods of palpitation which are described by a large percentage of patients.

4. The prognosis depends in a large measure on the condition of the circulation. If surgical treatment is to be carried out, the "time and extent of the operation should be governed by the circulatory condition."

5. Treatment of the thyroid heart depends on the stage of the disease. In all cases every measure should be employed to relieve the myocardium. Rest is essential. Sedative drugs are of some value. Elimination should be kept up. Digitalis is of great value in controlling auricular fibrillation and may be of value in preventing paroxysmal attacks. The amount required in controlling auricular fibrillation is usually less than in ordinary cardiac cases. It should be continued over long periods. Decompensation should be treated as in other myocardial cases.

6. The electrocardiogram is of value in recognizing myocardial changes, in differentiating the types of irregularities and in prognosis.

A CASE OF RHEUMATIC FEVER WITH CEREBRAL SYMPTOMS SIMULATING ENCEPHALITIS LETHARGICA

LEWIS FOX FRISSELL, M.D.

NEW YORK

History.—Mrs. J. F., aged 54, had a sharp attack of tonsillitis, Feb. 14, 1922, the temperature rising to 102.4 F., and culture showing *Streptococcus viridans*. Two days later she began to have joint pain, and large, elevated, red and tender nodes on the skin of the neck, and over the shins, typically an erythema nodosum.

Past History.—She had had typhoid fever, a severe case, at the age of 10, bronchopneumonia at 19, and frequent attacks of tonsillitis; headaches of a migrainal type, hemicranial in nature, with occasional hemianopsia.

She first consulted me in November, 1921, complaining of numbness and tingling in the arms, and legs, particularly in the left arm. One month before there was temporary loss of power of about one hour's duration. She was also confused mentally at this time. Her menstrual history began at 16, and was uneventful. Her marital history showed numerous miscarriages. She has one living, healthy child.

Physical Examination.—Patient was a slight, frail woman, with slightly coated tongue; a good deal of bridge work on the molar teeth, but no definite evidence of infection. Tonsils were small, buried, and contained cheesy particles. Pupils were equal, reacted to light and accommodation. Arteries of the retina were small and tortuous. Blood pressure was elevated; systolic, 204; diastolic, 108. Heart: Some left ventricular enlargement, with a systolic murmur at apex, transmitted to the left, and a sharply accentuated second aortic sound, and a second murmur over the aorta, transmitted to the vessels of the neck. The urine contained a very faint trace af albumin, but no casts; was of low specific gravity (1.010), but on the Mosenthal test (night specimen), showed that she still had ability to concentrate, and water produced a diuretic effect.

Blood chemistry was entirely normal. Blood Wassermann negative. Phenolsulphonephthalein, normal. A lumbar puncture was made with the idea of possible central nervous lesion, but the spinal fluid was completely normal. Wassermann, Lange's colloidal gold curve, butyric, and cells completely negative.

Diagnosis.—Cerebral arteriosclerosis, and chronic endocarditis.

Treatment.—She was put on proper diet, and made a symptomatic recovery within a few weeks.

Clinical Course.—Seven days following her acute tonsillitis in February, 1922, she began to show meningeal symptoms. Slight diplopia with left internal rectus muscle weakness, and an Oppenheim reaction were present, with doubtful Babinski, though no Kernig, and only very slight stiffness of the neck. Patellar reflexes were obtained. The areas of erythma nodosum were more numerous and painful. She had a slight dry, hacking cough, and an occasional fine subcrepitant râle in the right scapular region. Roentgenogram of lungs was negative. Her temperature was 103 F.; respiration, 30; pulse, 116. Her leukocytes numbered 18,000; polymorphonuclears, 87 per cent. Lumbar puncture revealed a fluid showing only two cells with a faintly positive butyric acid test.

The following day her meningeal symptoms were more marked. The patient became restless, and wildly irrational. Her neck was stiff. The left internal rectus muscle weakness was more marked, as was the Babinski, and the Oppenheim

reaction was more definite. Still no Kernig present. There were many fresh areas of erythema nodosum on both shins. Eyegrounds were negative except for vascular changes noted in November.

The following day the patient was semistuporous, the face showing the Parkinsonian masklike expression. Rigidity of neck continued. Babinski still present. Patellar reflex not obtainable. Blood culture and spinal fluid completely negative. At times there were severe pains running down the arms, of transitory duration, suggesting posterior root pain. At this time the patient presented an appearance fairly characteristic of encephalitis lethargica, but as it occurred in the course of rheumatic fever, and with a negative spinal fluid it was considered to be cerebral edema, with pressure on the optic thalami.

Owing to the uncertain diagnosis I requested Dr. Samuel Lambert to see her in consultation at 3 p. m. At 2 p. m. the patient's respiration had become difficult, she was completely comatose, recognizing no one. The nurse and family were much alarmed. When we saw her at 3 p. m., she was bright, and recognized everyone readily, talked without discomfort, though the Babinski and stiff neck persisted. February 25 slight facial weakness, and slight choreiform movements appeared. February 28, though her temperature was running a lower curve, the patient again became rather stupid, and did not cooperate well. She had slept most of the time for the past twenty-four hours. On March 1 she was seen in consultation by Dr. Foster Kennedy, who concurred in the diagnosis of encephalitis, not epidemic in nature. He also believed that her failure to cooperate and answer was due to an aphasia. Eyegrounds still remained normal.

On March 4 the aphasia was less marked and better cooperation could be obtained. She had no agraphia. March 12, there was slight diplopia, the margin of the right disk was slightly indistinct, and patellar reflexes had returned. By April 1 she had made a complete recovery. The cardiac signs remained unchanged throughout her illness.

CONCLUSION

This case is presented because of the particular interest attached to a diagnosis of a disease simulating encephalitis lethargica, but in all probability not etiologically related to it. The symptoms are believed to have been due to a localized edema of the brain, first in the thalamic region or falx, causing, by pressure symptoms typical of true epidemic encephalitis, and an aphasia due to a small localized edema in the speech area. The sudden remission of symptoms February 2, was due to the sudden disappearance of the edema, with consequent improvement of symptoms.[1]

1. Dr. Foster Kennedy has reported three cases of similar nature, Arch. Neurol. & Psychiat. **7**:53 (Jan.) 1922.

GRAVIMETRIC ESTIMATION OF PHOSPHATES OF THE BLOOD

PHOSPHATES IN NEPHRITIS *

WILLIAM J. FETTER, M.D.
PITTSBURGH

The methods at present employed for the estimation of blood phosphates involve the use of colorimetric or nephelometric determinations. Embden [1] recently described a technic for the gravimetric estimation of small amounts (from 1 to 4 mg.) of phosphoric acid in muscle. It seemed desirable to attempt to apply this method to the estimation of phosphates in whole blood. This method proved in use to be satisfactory, and it was then decided to apply it to the study of the phosphates in the blood in nephritis. The excretion of acid phosphate by the kidney is one of the chief lines of defence of the body against an abnormal accumulation of acid in the blood; moreover, the buffer action of the phosphates may help to keep the reaction of the blood within physiologic limits. In the latter mechanism it is obvious that only the inorganic phosphate in the blood can be concerned. It has already been stated by Marriott and Haessler [2] that the inorganic phosphates of the blood are increased in severe nephritis, but the relationship between inorganic and total phosphates in pathologic conditions has not been investigated so completely. It was, therefore, with the object of obtaining data on this point that the present investigation was undertaken.

EXPERIMENTAL

The method of Embden [1] for the estimation of phosphoric acid depends on its precipitation in the form of the complex alkaloidal salt strychnin phosphomolybdate. The weight of the precipitate obtained is equal to the weight of phosphoric acid present, multiplied by 28.24. A method essentially the same as this in principle has been applied by Bloor to the nephelometric estimation of phosphoric acid in blood but it will be seen from the magnitude of the above factor that from a relatively small quantity of blood, a sufficient precipitate can be obtained to weigh accurately. It seemed, therefore, reasonable to expect that the additional accuracy to be obtained by this gravimetric method would more than counterbalance the extra time expended in carrying it out.

* From the Department of Therapeutics, University of Edinburgh.

1. Embden: Ztschr. f. Physiol. Chem. **113**:138, 1921.
2. Marriott and Haessler: J. Biol. Chem. **32**:241, 1917.

Technic.—The technic of the method is as follows:

For the estimation of inorganic phosphate 5 c.c. of whole blood were employed. The blood was measured into a 50 c.c. flask and diluted to about 25 c.c. with warm water at a temperature of from 35 to 40 C. The diluted blood was allowed to stand fifteen minutes with frequent shaking to insure complete laking and 10 c.c. of an 11 per cent. solution of trichloracetic acid was then added. The contents of the flask were well mixed and diluted to the mark with water. After mixing and standing for a few minutes, the solution was filtered through a dry phosphate free filter paper. Twenty-five cubic centimeters of the water-clear filtrate was taken for the estimation, and sufficient water added to make the total volume, after the addition of the precipitating reagent, 75 c.c. The further steps will be described in connection with the estimation of total phosphates.

For the determination of total phosphates, 2.5 c.c. of whole blood were measured into a 25 c.c. flask and laked by dilution with warm water, as in the case of the inorganic phosphates. It was then made up to the mark and well mixed. Five cubic centimeters of this diluted blood was measured into a large silica test tube which had previously been cleaned by boiling strong sulphuric acid in it for twenty minutes. There was then added 2 c.c. of a

TABLE 1.—VALUE OF THE USE OF CANE SUGAR TO ASSIST COMBUSTION IN TOTAL PHOSPHATE ESTIMATION

Experiment	No Cane Sugar Used, Mg. H_3PO_4 per 100 C.c.	Cane Sugar Added, Mg. H_3PO_4 per 100 C.c.
1	123.9	119.6
2	125.3	112.6
3	139.5	128.8
4	124.5	133.1
5	127.4	124.6
6	118.2	128.8
7	133.1	125.3
8	79.3	69.4

mixture of equal parts of strong sulphuric and nitric acids and a few glass beads to prevent bumping. The combustion of the organic substances was carried out carefully in a manner which was virtually identical with that described by Bloor.[3]

The mixture was first raised to boiling and the flame was then turned down until only a slow bubbling took place. When most of the water had been driven off a small glass funnel was inserted into the mouth of the tube to eliminate all possibility of loss of contents by spurting and also to prevent the nitric acid from boiling off too quickly. Heating at this rate was continued until red fumes ceased to come off. The flame was then increased and strong heating was continued for from eight to ten minutes. In many cases the contents of the tube after this treatment retained still a yellowish tinge. If this were the case, a drop of strong nitric acid was added and the heating continued for one or two minutes. By this treatment complete clearing was obtained.

Bloor [3] recommends the addition at this stage of one or more drops of 1 per cent. cane sugar solution and subsequent reheating until the brown color caused by the addition of the cane sugar disappears. He

3. Bloor: J. Biol. Chem. **36**:33, 1918.

states that unless this precaution is observed, low results for phosphates are obtained. This point has been investigated and the results of analyses carried out with and without the use of cane sugar to assist the combustion are shown in Table 1. From these figures it appears that the results obtained without the use of cane sugar are, if anything, higher, but the difference is not very significant. The cane sugar, therefore, was not employed in the majority of the analyses recorded herein.

After completion of the combustion and cooling, the contents of the tube were thoroughly washed out with water into a 250 c.c. Erlenmeyer flask. Three drops of bromophenol blue were added to the solution and the solution was made alkaline with ammonia; dilute sulphuric acid was then added until the indicator just changed color. After thorough cooling, the solution was treated with the precipitating reagent, the total volume being made up to 75 c.c. The further technic is the same for the determination of both the inorganic and total phosphates.

The precipitating reagent employed was that described by Embden.[1] Two stock solutions were prepared—A, a solution containing 50 gm. of ammonium molybdate and 300 c.c. of concentrated nitric acid made up to 600 c.c. with water, and B, a 1.5 per cent. solution of strychnin nitrate. The actual precipitating reagent was prepared as required by mixing these solutions in the proportions of three parts of A to one part of B. For each precipitation 20 c.c. of the reagent were employed. The precipitating reagent was poured into the phosphate containing solution and the mixture was allowed to stand with frequent shaking for one hour, thus insuring complete precipitation. A yellowish, amorphous precipitate was obtained. At the end of one hour the contents of the flask were filtered through a Gooch crucible which had previously been dried at 110 C. and weighed. It is important to use only gentle suction during filtration. The precipitate was washed, first with 25 c.c. of ice cold diluted (1:5) molybdic-nitric acid reagent, and subsequently with ice cold water until the washings were no longer acid. The Gooch crucible was dried at 110 C. for one and a half hours, cooled in the dessicator and weighed.

The weight of the precipitate divided by 28.24 gives the weight of phosphate expressed as H_3PO_4. In most cases the weight of the final precipitate obtained was of the order of from 10 to 20 mg. and could, therefore, be weighed accurately with ease. With the quantities of blood usually employed this corresponds in the case of the inorganic phosphate to 2.5 c.c. of blood (5 c.c. of blood made up to 50 c.c.-25 c.c. of filtrate taken) and in the case of the total phosphate to 0.5 c.c. (2.5 c.c. of blood made up to 25 c.c.-5 c.c. of mixture taken).

For the success of this method it is important to use reagents of the highest purity. The estimations of inorganic phosphates in the blood should be done as soon as it is withdrawn or if this is impossible the blood should be kept on ice. Bloor [3] states that unless such precautions are observed fallacious results are obtained. This statement has been confirmed by actual experiment. As stated above, the use of cane sugar during the estimation of total phosphates does not appear to exercise a marked influence on the results obtained, but attention must be drawn to the fact that the most satisfactory results in the

recovery of added phosphates from the blood were obtained when cane sugar was employed (Experiments 3 and 4, Table 2-B.). Sufficient experiments have not been done to decide this point definitely.

In order to verify the accuracy of the method, a number of experiments on the recovery of added phosphate from blood were carried out and are recorded in Table 2. It will be seen that the calculated and

TABLE 2.—Estimation of Added Phosphates

Number	Added Phosphate Expressed as Mg. H_3PO_4 to 5 C.c. Blood (A) 2.5 C.c. Blood (B)	Phosphate in Blood, Mg. H_3PO_4 per 100 C.c.	Blood Plus Added Phosphate, Mg. H_3PO_4 per 100 C.c.	Calculated Blood Plus Added Phosphate, Mg. H_3PO_4 per 100 C.c.
A. Inorganic Phosphates				
I	7.3	11.92	159.6	158
II	6.55	4.53	137	136
III	7.9	14.8	172.2	172.8
B. Total Phosphates				
I	8.9	124.6	472.3	480
II	5.9	138.8	366.1	374.8
III	3.2	112.6	240	240.6
IV	6.0	119.6	355.5	359.6

observed results agree to within 1 per cent. in the case of the inorganic phosphate determinations, and to within about 2 per cent. in the case of the total phosphates. The greater error in the latter determination was probably due to the more difficult technic involved, as well as to the

TABLE 3.—Inorganic and Total Phosphates of Normal Whole Blood Mg. of H^3PO^4 Per 100 C.c.

Subject	Inorganic Phosphates	Total Phosphates	Subject	Inorganic Phosphates	Total Phosphates
1	10	.....	6	.....	128.8
	10	124		15	129.6
	9.6	.....	7	14.4	124.6
2	10.5	102		11.4	.....
	11.9	110.5	8	15.8	.....
	15.2	121		21.2	134.5
3	15	.....		18.8	138.8
4	13.3	135.9	11	14.8	116.8
5	....	119.6	12	....	133
	....	118.2		....	126.7
	....	122.5	13	....	135
	....	127.4	14	13.2	125
			15	....	123.9

smaller quantity of blood used. Nevertheless, the accuracy of the method is more than sufficient to meet the requirements of clinical estimations.

The phosphates of a group of normal adults were determined and the results will be found in Table 3. The samples of blood were drawn in the postabsorptive state to eliminate possible variations due to food. In one or two cases, several determinations were done on the same

TABLE 4.—Chronic Nephritis; Whole Blood

Case	Date	Age	Inorganic Phosphate, Mg. per 100 C.c. (H_3PO_4)	Total Phosphates, Mg. per 100 C.c. (H_3PO_4)	Ratio: Total to Inorganic	Non-protein Nitrogen, Mg. per 100 C.c.	Chlorids (NaCl), Mg. per 100 C.c.	Pressure CO_2, Mm. Hg	C.c. Vol. per Cent., CO_2, Taken Up	C.c. Vol. per Cent., CO_2, Normal (Haldane)	Alkaline Reserve, per Cent.	Phosphates in Urine, Gm. per Cent.	Phosphates in Urine, Gm. per Diem
1	10/17/21	72	12.6	118	9.3	50	547	53.8	58	57	+2		
2	10/22/21	68	13	127.4	9.7	48	585	43	52.7	52.5	±0	0.167	0.531
3	10/25/21	49	14.1	117.5	8.3	..	575	47	52.2	54	−3	0.115	1.93
4	10/27/21	55	14.8	114	7.7	40	562	42.7	54.3	52.5	+3	0.212	
5	10/31/21	13	13	121	9.2	40	531	46.4	57	54	+5	0.195	1.70
	11/ 1/21	..	19.8	128	6.5	..	....	45.1	53.5	53.5	±0		
	11/ 4/21	..	13.5	108.3	8	37	578	48.5	54.12	54.9	±0	0.230	2.07
6	11/ 2/21	21	13.7	122.5	8.9	..	511	50	52.21	55.3	−5	0.062	1.154
7	12/ 5/21	34	15.8	106.9	6.8	20	601	....	....	....	...	0.134	1.28
8	12/ 6/21	20	16.8	121.8	7.2	44	509	....	....	....	...	0.076	0.867
9	12/30/21	19	18.5	106	5.7	45	...	....	....	....	...	0.105	2.68
10	1/ 4/22	38	26.4	172	6.5	60	493.7	....	....	....	...	0.243	1.94
11	1/ 4/22	39	11 8	118.9	10	46	546	44.3	52.5	53	±0	0 067	0.714
12	3/17/22	24	15.2	111.2	7.3	34	563	34.7	49.1	48	+2	0.249	2.14
13	3/29/22	51	22.9	166	7.2	..	...	30.8	42.86	45.2	−5		
14	4/ 3/22	53	14	136.6	9.7	34	530	36.9	46.3	49.3	−6	0.087	0.935

Normal volume per cent. CO_2 in this table is that from the CO_2 dissociation curve of Haldane's blood, and the estimations were made with whole blood by a technic practically identical to that used by Christiansen, Douglas and Haldane (J. Physiol. **48**:244, 1914). The alkaline reserve is obtained by expressing the difference between volume per cent CO_2 found and the normal volume per cent. CO_2 as a percentage of the normal. It has been found in this laboratory that this notation is the most convenient and accurate, but the Haldane curve may not express the true normal for all individuals. There is reason to suppose that the limits of normality may be as much as 5 per cent. below the value found for Haldane's blood although we have seldom found values higher than those of Haldane in normal people.

subject and it will be observed in these cases that the results show but little variation, although considerable intervals of time elapsed between successive analyses.

In Table 4 are recorded the studies of fourteen cases of chronic nephritis. The diagnoses were based on clinical symptoms and signs, as well as on laboratory examinations of the blood and urine. In this table the phosphate values are correlated with those of the nonprotein nitrogen, chlorides, carbon dioxid combining power of the blood and the phosphates of the urine.

In Table 5 will be found similar determinations on six cases of acidosis, associated with nephritis, and one case (Case 7) of tetany with lowered alkaline reserve.

From a study of Table 1 the most noteworthy fact seems to be the relative constancy in the ratio of total to inorganic phosphate. This ratio averages about 8.5 to 1. The cases of chronic nephritis recorded in Table 4 show but little change in this ratio. In fact, there is but little difference between the results found in these cases of chronic nephritis and those for healthy persons. As a whole, there may be a slight increase in the inorganic phosphate and a slight decrease in the total phosphate. Patient 10 was a borderline case between an acute and chronic nephritis, having been quite ill before coming to the infirmary and very much improved when his blood was examined. Unfortunately, his alkaline reserve was not estimated, but his urine showed an acidity of 40 c.c. per cent. decinormal, and the ammonia nitrogen—urea nitrogen ratio was 0.13. The urinary acidity and the ammonia nitrogen and urea nitrogen were determined in the majority of these cases as a means to checking up the alkaline reserve. Patient 13 gave a history of having had clinical signs of acidosis before admission to the infirmary but the alkaline reserve proved to be nearly normal. Therefore, with but a small increase in the nitrogen retention, a normal or nearly normal alkaline reserve, a low output of acid in the urine and an ammonia nitrogen—urea nitrogen ratio approaching 0.03, the inorganic and total phosphates of blood do not vary considerably from the normal.

A study of the more severe cases of nephritis, those with uremia and acidosis, revealed an interesting change in the phosphorus compounds of blood. Invariably there was a marked increase in the inorganic phosphate, accompanied often by a slight decrease in the total phosphates, resulting in a low ratio of total to inorganic phosphates.

DISCUSSION

The general deduction from the results recorded above seems to be that the phosphates in the blood in nephritis only show a marked variation from the normal when the condition is associated with acidosis. In cases of acidosis, the inorganic phosphates are almost constantly

TABLE 5.—Nephritis with Acidosis; Whole Blood

Case	Date	Age	Inorganic Phosphate, Mg. per 100 C.c. (H_3PO_4)	Total Phosphates, Mg. per 100 C.c. (H_3PO_4)	Ratio: Total to Inorganic	Non-protein Nitrogen, Mg. per 100 C.c.	Chlorids (NaCl), Mg. per 100 C.c.	Pressure CO_2, Mm. Hg	C.c. Vol. per Cent., CO_2, Taken Up	C.c. Vol. per Cent., CO_2, Normal (Haldane)	Alkaline Reserve, per Cent.	Phosphates in Urine, Gm. per Cent.	Phosphates in Urine, Gm. per Diem
1	10/20/21	65	34.9	108.3	3.1	124	609	50.6	32.1	55.5	—42		
	10/21/21	..	35.7	113.3	3.2	...	...	....	....	....	....	0.123	1.37
	10/25/21	..	37.2	114.7	3	126	678	43	28.7	52.5	—45	0.091	0.355
2	11/ 7/21	58	20.4	121.1	5.9	96	578	38.3	43.5	50.1	—13	0.061	0.663
	11/ 9/21	..	20.3	.....	...	92	...	40.1	42.7	51	—16	0.086	0.834
	11/12/21	..	21.5	121.8	5.6	...	...	35.6	45.2	48.6	— 7	0.087	
	11/17/21	..	25.2	114	4.5	...	593	43.1	53.2	52.5	± 0	0.126	1.15
3	11/14/21	40	42.2	149.6	3.5	160	562	42.1	37	52	—28	0.055	1.106
	11/16/21	..	44.1	173.5	3.9	191	578	29.9	28.4	45.3	—37		
4*	11/15/21	41	43.6	116.2	2.6	148	576	44.5	28.3	53.1	—47	0.056	0.494
	11/22/21	..	28.3	111.1	3.9	132	...	....	....	....	. ..	0.062	0.615
	11/28/21	..	17.9	101.2	5.6	94	578	38.05	67.3	49.9	+37	0.03	0.540
5	12/ 1/21	41	27.34	.....	...	106	553	40.7	37.7	51.3	—26	0.058	0.769
	12/ 8/21	..	31.4	101.9	3.2	116	568						
	12/14/21	..	32.1	126.7	3.9	210	546	42.3	42	52.1	—19	0.069	
6	2/15/22	38	25.7	123.2	4.7	70	594	42.2	44.8	52	—14	0.095	1.909
	2/27/22	..	14.8	79.3	5.3	67	547	42.5	45.6	52.2	—12	0.055	1.947
7	3/ 8/22	40	25.9	97.7	3.7								
	3/10/22	..	24.6	92.7	3.7								
	3/23/22	..	28	.....	...	...	...	42.8	35.3	52.3	—33		

* This patient had been put on intensive treatment with sodium bicarbonate thus producing the alkalosis.

increased above the normal value, sometimes to a considerable extent (Cases 1, 3 and 4, Table 5). This increase may be associated with an increase in the total phosphate (Case 3, Table 5) or the total phosphate may be normal or even low. The high values of the inorganic phosphate suggest strongly that this substance is being mobilized to maintain the reaction of the blood within physiologic limits.

The fact that some cases show high values for total phosphates, and other cases show low values may be accounted for in the following way: It is possible to conceive of two types of acidosis which may be brought about by a disturbance in the normal function of phosphates in the body. Either the kidney may lose the power of excreting phosphate, in which case acid phosphate would be retained in the blood thus producing a true "phosphate acidosis," as indicated by high total phosphates, or, owing to the abnormal rate of production of acids in the body or the failure of other mechanisms for their excretion (e. g., the excretion of ammonium salts by the kidney), the phosphates of the body may be used up at such a rate for the purpose of excretion of acid that the total store of phosphates becomes depleted. The first type is represented by Case 3, Table 5, and the second type by Cases 1, 2 and 7. In Case 2 the patient was treated with disodium phosphate (4 drams daily from the tenth). It will be seen that on this treatment the alkaline reserve returned to normal, and coincidentally the output of phosphate in the urine increased. Presumably, therefore, in this case the excretion of acid had become deficient owing to depletion of the phosphates of the body and this condition was relieved by the oral administration of phosphate.

In connection with this may be mentioned a case of acute nephritis in a child which was admitted to the Royal Infirmary before this investigation took place. This patient on admission showed a severe nitrogen retention and acidosis, the output of phosphate in the urine being very much reduced. The laboratory findings are recorded in Table 6. On the assumption that the acidosis was due to depletion of phosphate, disodium phosphate, in doses of 30 grains, every two hours, was administered. On this treatment the condition of the patient rapidly improved, the acidosis disappeared and a laboratory examination two weeks later showed normal values for the nitrogen of the blood and an enormous increase in the output of phosphate in the urine.

The administration of calcium has been suggested by Marriott and Howland [4] to relieve retention of phosphates. According to the hypothesis outlined above, this treatment would be indicated only in cases such as Case 3, but so far it has not been possible to obtain data on this point.

4. Marriott, W. McK., and Howland, J.: Phosphate Retention as a Factor in the Production of Acidosis in Nephritis, Arch. Int. Med. **18**:708 (Dec.) 1916.

TABLE 6

Observation No.	Date	Urine						Blood				Remarks
		C.c. per 24 Hours	Ammonia Nitrogen, Mg. per Cent.	Urea Nitrogen, Mg. per Cent.	Acidity, per Cent. of N/10 Acid	NaCl, Mg. per Cent.	P_2O_5, Mg. per Cent.	Total Non-protein N Mg. per Cent.	Urea Nitrogen, per Cent.	NaCl, Mg. per Cent.	Alkaline Reserve Percentage Deficiency	
1	6/10/21	277	4.9	182	16	131	70	222	180	484	−22	Schoolgirl, age 12; admitted June 9, 1921, for acute recurrence of old nephritis; albuminuria, hematuria, vomiting, headache; no edema; slight but definite hyperpnea
	6/11/21	.....	....	...	..	...	...	...	...	...	....	Commenced Na_2HPO_4, 30 grains every two hours
2	6/13/21	560	7.7	395	15	157	90	278	208	477	± 0	No hyperpnea
	6/16/21	.....	....	...	..	...	...	...	...	...	....	Urine volume per day doubled; specific gravity remaining the same; erythematous rash all over body
3	6/29/21	1,130	5.6	281	10.4	353	225	36	28	556	+ 9	Na_2HPO_4 stopped
4	7/15/21	642	17.5	871	33	501	170	35	28	538	− 3	Much improved
5	9/ 4/21	.....	....	...	..	...	...	36	...	563	....	Albuminuria and hematuria almost disappeared; patient discharged from hospital

SUMMARY

1. A gravimetric method for the estimation of the inorganic and total phosphates in whole blood is described.

2. The results are recorded of a number of analyses carried out on normal persons, cases of chronic nephritis and cases of nephritis with acidosis.

3. A suggestion is put forward as to the line of treatment to be adopted in relation to the findings of blood phosphates.

THE INCREASE OF CERTAIN VAGAL EFFECTS WITH INCREASED AGE *

N. C. GILBERT, M.D.
CHICAGO

During the course of a consideration of the occurrence of respiratory arrhythmia in old age, it became evident that there was an increase in certain vagal effects, coincident with increased age.

That there is such an increase in vagal activity, is not a new observation. Mention of such an increased activity has been made from time to time, but little definite evidence is to be gained from the literature.

Allbutt [1] predicates such an overaction of the vagus with age. He cites Dr. Hugh Anderson's experiments showing an increased vagus action in old cats and not in young kittens. He also quotes Wenckebach's observation that he had found the vagus especially active in anginal cases. More recently Vinnes [2] has shown that the effect of pressure over the vagus trunk was more pronounced in adults than in children. Glaser,[3] however, by a different method, concludes that the vagus is more active in youth, and less active in old age.

In testing the response of the heart to stimulation of the vagus trunk as it descends in the neck beside the carotid, we had noticed certain differences in the degree of response which we thought to vary with age, and at that time, with cardiac pathology. In order to determine just what were the factors which influenced the degree of response, the reaction was measured and tabulated in a series of 177 cases, the patients ranging in age from 5 to 93.

Mechanical stimulation of the vagus by pressure over the nerve as it descends in the carotid sheath is a procedure which has been familiar since its description by Czernak about half a century ago, and requires no comment. Its disadvantages are certain very obvious inaccuracies. It is quite possible that in some cases the nerve may escape stimulation altogether. The moment of stimulation, the duration, or the intensity cannot be determined with accuracy. It cannot be deter-

* From the Medical Service of St. Luke's Hospital.

1. Allbutt, C.: Diseases of the Arteries and Angina Pectoris, London, 1915.

2. Vinnes, E. M. G.: Genessk. bladen **22**:41, 1920; rev. in Physiol. Arch. 6:40, 1921.

3. Glaser, F.: Med. Klin., **18**:371, 1922.

mined whether the effect is through a peripheral action, whether it is central through the opposite nucleus, or whether it is peripheral in one instance, and central in another.

In the cases here recorded the electrographic string was watched, and stimulation discontinued the moment any effect was noted. Minimal pressure was used at first, and in many cases, especially in the sixth decade, it was instantly productive. If no effect was observed, pressure was increased, or the position changed. The time of stimulation was recorded on the tracing, but was given no weight.

There were no uncomfortable sequels. Some patients were momentarily unconscious, but were not aware of it themselves, and felt no ill

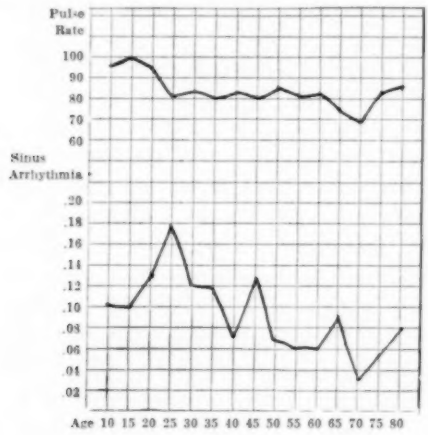

Fig. 1.—Pulse rate and the degree of sinus arrhythmia averaged in five year periods and plotted according to age.

after effects. So far as I have been able to discover, no serious results are recorded in the literature. Robinson [4] comments on the safety of the procedure. Wenckebach,[5] with a large experience, observed no ill effects but used great care. My own faith in the certainty of the heart to escape from vagal stimulation was considerably shaken by one case early in the series. A man, aged 65, after very light and momentary pressure, had a complete standstill, with no ventricular escape for 5.76 seconds, when the normal sequence returned. Wenckebach records

4. Robinson, G. C., and Draper, G.: J. Exper. M. **14**:217, 1911; **15**:14, 1912.

5. Wenckebach, K. F.: Die Unregelmässige Hertztätigkeit, Leipzig u. Berlin, 1914.

a standstill of 6 seconds, as does Vinnes. I do not feel that the procedure is without the possibility of danger. In our cases in the fifth decade and past we erred on the side of safety, and used lighter pressure.

To secure those with normal hearts, chosen cases from the surgical and orthopedic wards, hospital attendants, physicians and students were used. A normal tracing was taken with all three leads, followed by a strip of Lead II taken during forced deep respiration. A tracing of Lead II was then taken during stimulation of the right and left vagus, or the tracings were taken in the reverse order.

Measurements were made to 0.01 seconds, which allowed of more than sufficient accuracy where the deviations were so extreme.

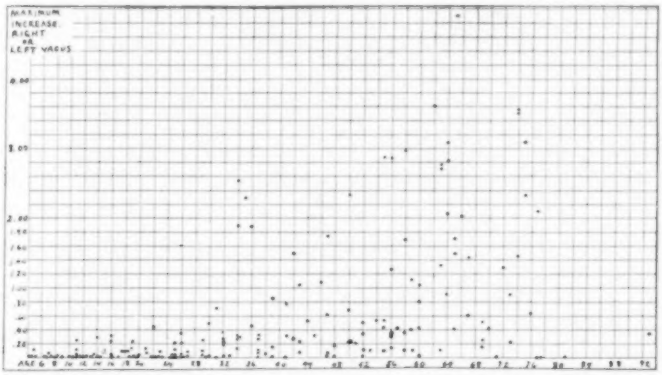

Fig. 2.—Maximum increase in the *R-R* interval obtained by digital stimulation of either vagus, plotted in hundredths of a second, according to age.

Pulse Rate.—The relation of pulse rate to age in this series is shown in Figure 1. The rates are averaged in five year periods. In so small a series the resulting curve is, of course, very uneven. It shows, however, a definite decrease in rate to the age, 65-70, followed by a rise. This agrees with the table compiled by Guy [6] and summarized by Howell.[7]

Sinus Arrhythmia.—The degree of respiratory arrhythmia was measured by the difference in length between the longest and the shortest *R-R* intervals in the normal tracing. Because of the small number of cases, we again have a very irregular curve, but the ten-

6. Guy: In Todd's Cyclopedia of Anatomy and Physiology, London, 1847.

7. Howell, W. H.: Textbook of Physiology, W. B. Saunders Company, Philadelphia, 1915.

dency to decrease with age is unmistakable. The increase in the degree of respiratory arrhythmia in forced deep respiration followed a similar curve.

EFFECT OF DIGITAL STIMULATION OF RIGHT AND LEFT VAGUS

The degree of effect of vagus stimulation was measured by the difference in length between the longest *R-R* interval in the normal tracing, and the longest *R-R* interval obtained on vagus stimulation. The *P-P* interval frequently was longer than the *R-R* interval, but was not used because of the difficulty of determining in many cases whether the intervening ventricular complexes were in response to impulses generated low down with an iso-electric *P* wave, or whether they were actual ventricular escapes.

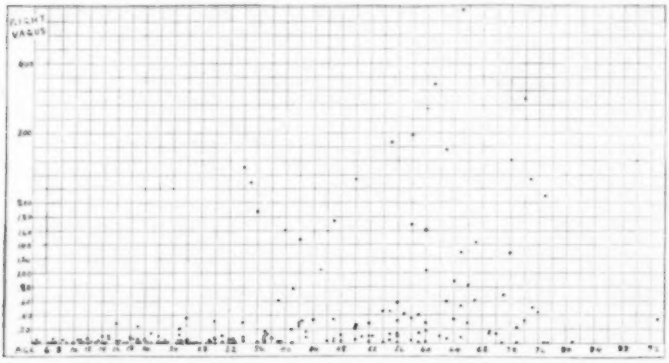

Fig. 3.—Maximum increase in the *R-R* interval obtained by digital stimulation of the right vagus, plotted in hundredths of a second, according to age.

A discussion of the variation in vagus effects on stimulation would require a more detailed analysis than can be given here. There was no marked difference between the right and left vagus. The predominating effect was a slowing of stimulus production, frequently with a decrease in amplitude of the *P* wave, which in some of the cases became iso-electric or inverted. As the pace-maker was displaced downward, a decrease in the *P-R* interval was noted in part of the cases. In some of the younger subjects there was a generalized slowing of rate, although the *R-R* intervals were no longer than the longest observed before the stimulation.

An increase in the *P-R* interval of 0.01 second or more was present in less than one third of the cases. Complete disassociation occurred in one case with both right and left vagus stimulation in a case of 2 to

1 block, and in two cases with right vagus stimulation, and in two cases with left vagus stimulation. All of the subjects showing complete block had definite cardiac pathology, and all were over 60, except one, aged 34.

The difference in 0.01 seconds between the longest normal *R-R* interval and that obtained on vagus stimulation was plotted according to the age of the subject.

In Figure 2 is plotted the maximum increase with either vagus, and in Figures 3 and 4 the increase with the right and left vagus is shown, respectively. The three figures are quite similar, and show an increase in response with increased age, with the possibility of a decrease in the latter part of the seventh decade and after.

That the increase in response is a function of the age of the subject,

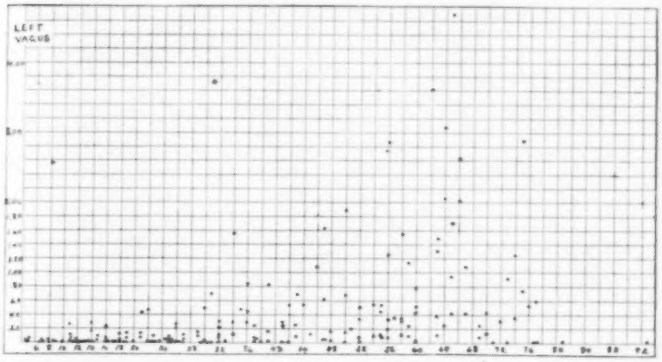

Fig. 4.—Maximum increase in the *R-R* interval obtained by digital stimulation of the left vagus, plotted in hundredths of a second, according to age.

and not of the cardiac pathology, is indicated in Figures 5 and 6. In these charts are plotted separately the results obtained in cases presenting definite pathology and those with no demonstrable pathology. The maximum response with either right or left vagus is plotted.

It is difficult to say that any person past middle life has a normal heart, or what is normal for the age. We can only say in the cases used in this series that they had no circulatory symptoms or demonstrable findings. Arteriosclerosis was present in varying degree in both series. Functional kidney tests (phenolsulphonephthalein) and blood chemistry were within normal limits in the cases charted as normal. The two charts are again essentially alike, and show only an increase in response with increased age.

In Figures 7 and 8 are plotted the changes in conduction time with right and left vagus. Decreases in the *P-R* interval are plotted below

the base line, and increases in the *P-R* interval are shown above the baseline in 0.01 seconds, according to age. Here, again, an increase in response is seen with increased age, as indicated by an increase in the *P-R* interval. Cardiac pathology could not be demonstrated to be a factor in the decrease of conductivity, although it is to be noted that all of the cases, except one of those showing complete block, were cases manifesting definite cardiac lesions. It is possible that in a larger series a more definite difference could be noted in the effect on conductivity.

The heart cases were such as are usually found in the wards of a large city hospital, and represented all degrees of circulatory insuf-

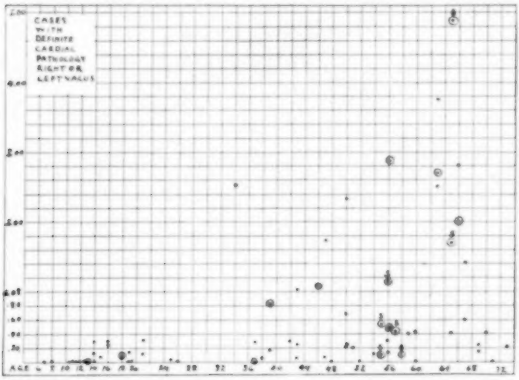

Fig. 5.—Maximum increase in the *R-R* interval obtained by digital stimulation of either vagus in patients who showed a definite pathologic cardiac condition, plotted in hundredths of a second, according to age.

ficiency. No relation could be demonstrated between the anatomic lesion, the severity of the lesion, or the degree of circulatory disturbance and the vagus effect.

It is difficult to evaluate arteriosclerosis accurately. The degree of arteriosclerosis was apparently not a factor. High or low blood pressure was not a factor.

In general, but not invariably, the patients who were well under the influence of digitalis showed an increased effect. One subject, a boy, aged 12, suffering from mitral stenosis with auricular fibrillation, who entered the hospital with extreme evidences of circulatory insufficiency, showed no response on entrance, but a moderate response when under the influence of digitalis.

The cases showing other evidences of overactivity of the vagus frequently, but not invariably, showed an increased effect.

A consideration of individual cases renders it even more difficult to see that cardiac pathology has any bearing on the degree of vagus effect. A subject with a mitral lesion, aged 37, who was moribund, showed no effect. A similar subject, aged 46, showed a marked effect. A patient with carcinoma of the stomach, aged 54, with generalized metastases, showed a well marked effect two hours before death. One patient, aged 66, showed a marked effect when apparently well, and no effect later, when moribund with a nephritis. The angina pectoris patients showed an effect proportionate to the expectancy for the age, and no more. Some patients with marked angina showed no effect.

There would seem to be no relation between the degree of vagus effect and prognosis. In the eighteen months of observation there have been no deaths in the group with increased response and no

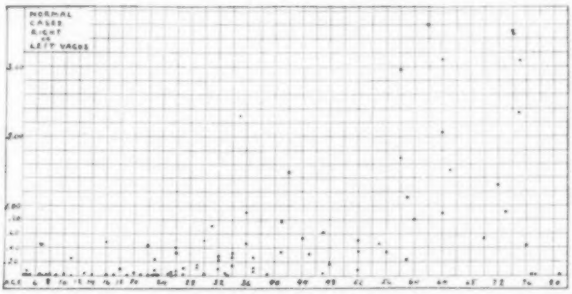

Fig. 6.—Maximum increase in the *R-R* interval obtained by digital stimulation of either vagus in patients who showed no demonstrable pathologic cardiac condition, plotted in hundredths of a second, according to age.

cardiac pathology. Of the group suffering from cardiac disease, fifteen have died. These are indicated by a circle in Figure 5. They are about equally distributed between those cases showing slight or no effect, moderate effect and marked effect. In the case of patients dying suddenly and unexpectedly, the circle is surmounted by an *S*. Here, again, the vagus effect is not a factor, but an analysis would demand an accurate knowledge of the mechanism of the death in each case.

The foregoing does not agree with the conclusions of Wenckebach, who considers that an increased reaction is indicative, but not invariably so, of pathologic changes in the cardiac muscle, and who is inclined to give a bad prognosis when a marked effect results from light pressure. It is interesting to note that the cases figured by Wenckebach fall within the ages when a marked response would be expected in either normal or abnormal hearts, according to the results shown here.

Hough [8] with experimental cats and dogs under anesthesia showed an increased effect when the heart was weakened by long experiment. The anesthetic, however, introduces an unknown variable, as shown by Becht.[9]

The question as to whether the increased effect of vagus stimulation with increased age is due to increased central activity or to peripheral changes involving the nerve endings or to changes in the tissues effected is of interest. It is also conceivable that it could be due to a decrease in the activity of the sympathetic system. If there be a decrease of sympathetic activity with age, we know nothing of it at present.

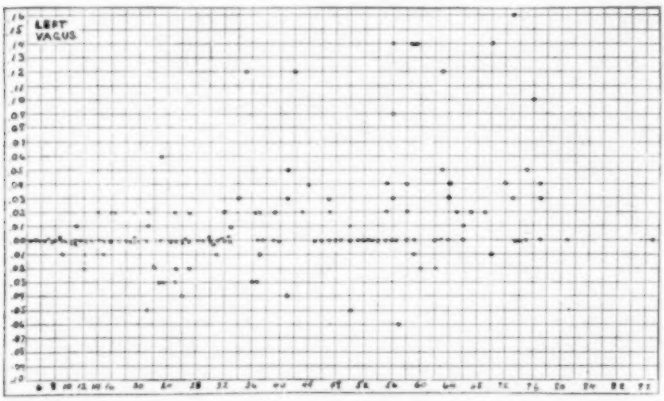

Fig. 7.—Changes in the *P-R* interval obtained by digital stimulation of the left vagus, plotted in hundredths of a second according to age. Increases in the *P-R* interval are plotted above the base line, and decreases in the *P-R* interval are plotted below the base line.

In the consideration of an increase in central activity of the vagus, an argument based on overactivity in other organs would again require proof that such an overaction was based on central and not peripheral changes. The pulse is slower with age up to a certain point, but such a slowing is not necessarily a central phenomenon. If there were an increased central activity of the vagus we might expect to obtain vagus effects with smaller doses of digitalis in later life. This was not the observation of Eggleston,[10] who found a very slightly increased dosage necessary after 40. My personal observation is that the dosage is the same. The validity of this argument, however, depends on the physics of digitalis action.

8. Hough, T.: J. Physiol. **18**:161, 1895.
9. Becht, F. C.: To be published.
10. Eggleston, C.: Digitalis Dosage, Arch. Int. Med. **16**:1 (July) 1915.

Wenckebach concludes that the cause of the increased reaction lies in changes in the reacting tissue, consequent on pathologic changes in the tissue. If disease is a factor at all, it is not a simple factor. Age quite apparently is a factor, and it is quite possible that there may be changes coincident with age in either the nerve endings or in the reacting tissues, which results in a so-called lowering of the neuromuscular threshold. It is interesting in this connection to recall the variation in atropin effect with age. The effect of atropin is on the vagus nerve endings. After paralysis of the vagus nerve endings with atropin, there is an increase in the degree of acceleration of the pulse up to the age of 30, and then a decrease, until in old age there

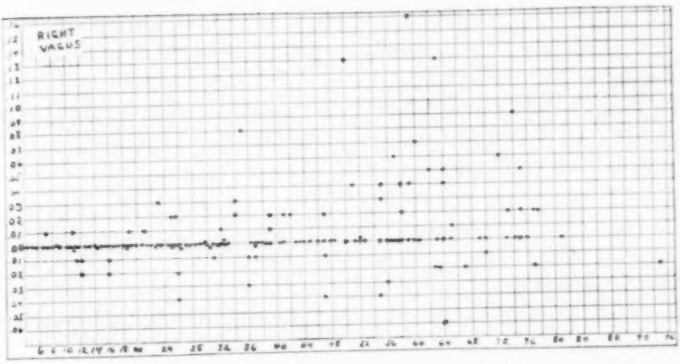

Fig. 8.—Changes in the *P-R* interval obtained by digital stimulation of the right vagus, plotted in hundredths of a second according to age. Increases in the *P-R* interval are plotted above the base line, and decreases in the *P-R* interval are plotted below the base line.

is little or no acceleration (Cushney[11]). In my own experience there is little or no acceleration after the fifth decade, and exceptions are rare, although they do occur. This would, of course, argue equally well for a decrease in sympathetic activity, if we had any other evidence of such a decrease.

Respiratory arrhythmia, and the increase in this arrhythmia with increased ventilation of the lungs, shows a decrease with age. This might be construed as indicating a decrease in the central activity of the vagus. But it is to be remembered that while such arrhythmia depends on the activity of the vagus nucleus for its appearance, it is not purely a vagus phenomenon, and that other factors not checked here enter into its appearance.

11. Cushny, A. R.: Textbook of Pharmacology and Therapeutics, Philadelphia, Lea and Febiger, 1918.

The preponderance of the little evidence we have appears to be in favor of the increased activity being due to changes in the nerve endings or the reacting tissues. Proof will depend on animal experiment.

The fact of such an increased vagus effect accompanying increased age opens a wide field of possibilities, on which we will not attempt to speculate. Such variations with age and with other pathologic or normal changes in tissues are of immediate physiologic and clinical importance.

A point of especial interest in the present instance is the bearing on the increased liability to the "vagal death" of Allbutt, and Capps and Lewis,[12] and on the hypotheses of Verdon.[13]

One would like to regard the increased vagus effect as conservative in character. It is possible that it might be regarded as one factor in a more labile depressor mechanism. Should we accept the theories of Hering and of Gaskell there would be a tendency toward an increase of the anabolic processes with age. In the light of our present knowledge, however, any comment on the significance of this phenomenon is treading on unsafe ground.

SUMMARY

1. In a series of 177 cases, the subjects ranging in age from 5 to 93 years, there is shown to be an increase in the response of the vagus to digital stimulation coincident with increased age.

2. This increase is a function of age alone and not of pathologic changes in the heart.

3. Whether the increase is due to central changes or to peripheral changes in the vagus or tissues affected cannot be proved from the evidence at hand.

12. Capps, J. A., and Lewis, D.: Am. J. M. Sc. **134**:130, 1907.
13. Verdon, W.: Angina Pectoris, London, 1920.

STUDIES OF EXOPHTHALMIC GOITER AND THE INVOLUNTARY NERVOUS SYSTEM

LEO KESSEL, M.D., CHARLES C. LIEB, M.D.
AND
HAROLD T. HYMAN, M.D.

III. A STUDY OF FIFTY CONSECUTIVE CASES OF EXOPHTHALMIC GOITER

LEO KESSEL, M.D., HAROLD T. HYMAN, M.D.
AND
HERMAN LANDE, M.D.*
NEW YORK

INTRODUCTION

This report is a detailed account of the course of fifty cases of fully developed exophthalmic goiter. In order to eliminate the personal factor in diagnosis, no patient was included in this group in whom the clinical diagnosis was not confirmed by a distinct and continuous elevation of the basal metabolism. The course of the illness was followed with as little interference with the natural tendency of the disease as was compatible with the comfort of the patient. While of course, this could not be accomplished in as clearly defined a manner as the maintenance of a laboratory control, at least it is true that in these patients no specific therapy was instituted. The course of the symptoms and of the basal metabolism was closely followed, and the results obtained were estimated on the basis of restoration to social and economic usefulness, and on the return of the metabolism to within normal limits.

The observations made on this group of patients is the first step in the crystallization of a definite therapeutic policy for exophthalmic goiter, for with the establishment of the spontaneous course it will be possible in future studies to evaluate accurately the efficacy of "specific" therapeutic procedures.

In the two papers[1] that precede this one will be found a description of two groups of patients often erroneously included in reports dealing with exophthalmic goiter. The first group included patients who have a lump in the neck, and who have none of the primary or secondary manifestations of exophthalmic goiter, and no elevation of the basal metabolism. In the second group were patients who, with or without thyroid enlargement, presented symptoms and signs best

* Dr. Lande is solely responsible for the metabolic studies in this as in the preceding papers.

1. Kessel and Hyman: Am. J. M. Sc. To be published.

TABLE 1.—A Symptomatic, Metabolic and Economic Study of the Results Obtained in Fifty Consecutive Cases of Graves' Syndrome Observed Without the Institution of "Specific" Therapy ("Spontaneous Course")

Case Number	Social or Economic Status	Period of Observation					Period to Secure Complete Social or Economic Restitution, Months	Basal Metabolism				Number of Subjective Symptoms		Severity of Subjective Symptoms		Decrease of Neck Circumference, Cm.	Increase in Weight, Lbs.	Remarks
		Total, Months	Weeks in Hospital	Weeks in Country	Months at Home, Full Rest	Months at Home, Part Rest		First	Lowest	Percentage of Decrease	Period to Obtain Decrease, Mos.	(a) On Admission	(b) At Last Visit	(a) On Admission	(b) At Last Visit			
1	Clerk	19	3	0	0	0	1	37	14	62	13	5	0	9	0	2	..	Lost from observation for a year during which time he worked. Now reports
2	Peddler	8	2	0	0	0	1	45	16	65	3	11	4	24	4	6	20	Works from 5 a.m. to 9 p.m. with only a few hours rest in between
3	Peddler	13	8	0	0	0	2	26	18	30	2	10	1	32	1	3	12	Has moved to Detroit. Have not heard from him in 4 months
4	Jeweller	18	8	8	0	0	4	47	29	57	2	1	0	4	0	6	5	Has developed migrainous headaches
5	Foreman	16	4	0	0	0	?	39	31	20	5	6	0	15	0	3	..	Had severe pneumonia. Have not seen him in 5 months
6	Clerk	20	10	5	0	0	4	54	16	70	3	12	1	26	3	0	53	Had true febrile recurrence following tonsillitis. Now receiving Roentgen ray at P. H.
7	Baker	12	12	0	1	0	4	35	16	55	3	6	0	14	0	..	22	Working 10 hours a day
8	Cobbler	..	..	..	..	..	Died	75	..	..	..	..	..	..	..	..	..	Died of exophthalmic goiter. Febrile crisis
9	Operator	..	..	..	..	..	Died	..	..	..	..	..	..	..	..	..	..	Died of hemorrhage from cancer of stomach.
10	Operator	13	1	3	1	0	2	38	..	..	..	..	..	..	..	..	..	Has been working for several months
11	School	11	6	4	1	0	5	8	4	..	2	8	1	25	1	..	..	Had pneumonia. Complete recovery
12	Clerk	20	3	0	1	3	14	25	12	52	3	2	2	17	1	4	11	Has had three sinus operations each accompanied by slight exacerbation
13	Typist	10	9	8	1	0	10	40	28	30	2	10	3	8	8	4	14	Prolonged course. Now looking for employment
14	Operator	3	5	6	0	0	Died	44	40	9	1	10	2	36	5	5	25	Died of status lymphaticus after losing most of manifestations of exophthalmic goiter
15	Painter	19	6	4	0	0	4	53	6	88	3	9	0	19	3	..	..	Working for 15 months
16	Typist	10	5	5	0	0	3	18	5	100	1	12	1	24	0	..	16	Working for 5 months
17	Housewife	7	6	1	3/4	0	3	58	44	24	4	14	4	21	1	..	6	Symptoms greatly improved although basal metabolism elevation persists
18	Clerk	7	9	2	0	0	7	57	15	73	4	14	1	39	5	6	24	Working
19	Nurse	2	9	..	..	..	..	24	19	21	1	7	2	45	1	4	24	Lost from observation
20	Operator	22	4	5	0	3	15	35	3	89	7	5	1	18	5	..	..	At work
21	Operator	22	8	4	0	½	3	55	0	100	8	8	0	10	1	2	..	At work for over a year
22	Typist	10	6	4	0	0	3	46	15	67	3	13	5	16	0	5	20	At work
														33	5	6	23	

23	Housewife.....	7	4	0	0	1	2	20	15	25	4	13	2	25	2	4	6	Has had trying home conditions
24	Housewife.....	18	3	3	0	0	2	17	5	71	3	12	0	16	0	1	10	Had a mastoiditis
25	Housewife.....	13	10	4	0	½	13	34	17	50	2	10	3	30	6	3	11	Basal metabolism rose to 44 with sinusitis. Great relief to exophthalmic goiter with sinus treatment
26	Teacher.....	13	4	12	6	1	11	29	8	72	3	9	0	22	0	6	10	To be married
27	Housewife.....	12	7	0	0	3	5	48	26	45	2	7	3	14	3	6	15	Has mitral stenosis and most symptoms are cardiac
28	Housewife.....	14	3	4	0	2	?	64	22	66	7	14	4	35	4	6	10	An unmanageable person. Has run varied career. At present is well
29	Housewife.....	13	6	0	2	2	12	100	9	91	9	4	1	7	1	3	20	Marked goiterophobia
30	Housewife.....	18	6	6	0	0	3	64	15	77	12	13	1	21	1	4	16	Has remained well through a pregnancy and terrific financial straits
31	Teacher.....	13	7	7	0	1	5	58	12	80	8	16	2	36	4	2	36	Laryngeal symptoms most marked. Improved somewhat by vocalist
32	Housewife.....	10	4	1	0	0	2	50	20	60	3	15	1	27	1	1	21	Exophthalmometer reading decreased 5 mm.
33	Dancer.....	13	4	0	0	12	3	40	14	65	1	8	0	14	0	..	..	Though symptom free and with normal basal metabolism, had thyroidectomy for cosmetic reason
34	Housewife.....	14	4	20	0	1	6	36	4	89	2	5	1	13	1	..	5	Severe mental and economic strain, but keeps fairly fit
35	Homeworker...	17	4	8	0	0	3	22	16	27	1	5	1	14	1	9	17	Has healed tuberculosis
36	Housewife....	21	6	0	½	2	6	48	17	65	1	14	0	40	0	..	38	Marked weight gain
37	Housewife.....	17	5	2	0	1	2	35	12	66	1	9	1	25	1	5	..	Has gone through normal pregnancy and sinus infection with only slight exacerbation
38	?.....	..	..	..	..	..	Died	62	..	..	..	..	..	..	..	..	..	Febrile psychosis. Sent to Bellevue where she died
39	Housewife.....	16	0	0	0	0	0	37	6	84	9	7	5	24	11	..	..	Has had twins. Economic struggle keen
40	Housewife.....	19	42	12	0	0	4	30	17	43	1	8	1	24	1	..	7	Has gone through normal pregnancy
41	Housewife.....	17	4	0	0	0	2	48	6	89	5	7	2	15	2	4	4	Still complains of gastro-intestinal symptoms
42	Housewife.....	8	9	4	½	0	3	68	41	40	4	17	6	50	10	3	10	Persistent elevation of basal metabolism despite improvement clinically
43	Housewife.. ...	9	6	0	0	1	3	47	0	100	8	12	9	35	11	6	15	Symptoms greately increased by sinus infection and abate with drainage
44	Pianist.....	19	2	0	2	½	3	63	0	100	7	7	0	18	0	..	14	Extraordinary recovery
45	Housewife.....	12	2	4	0	0	2	28	6	79	3	8	2	18	4	..	25	Great mental and economic stress. Had transient fibrillation
46	Housewife.....	10	17	0	2	0	..	50	31	38	6	13	2	27	2	3	..	Had hydrops of gallbladder. Economically unfit
47	Peddler.....	12	5	4	0	0	2	47	14	66	9	7	2	18	4	..	15	An epileptic
48	Janitress.....	7	9	8	5	0	..	48	43	10	2	8	1	26	4	..	..	Has decompensated myocardium and auricular fibrillation
49	Janitress.....	2	9	..	..	.	Died	50	24	52	2	..	..	..	..	..	..	Died of pneumonia and pericarditis following pyelitis
50	Housewife.....	2	10	..	..	..	..	48	48	..	..	..	..	..	..	..	..	Failure. Lost from observation
51	Housewife.....	7	21	9	..	..	..	57	62	..	..	13	5	38	10	..	..	Persistent fibrillation, diarrhea and elevated basal metabolism, but clinically better

grouped under the single term of "sympathomimetic," the term of Barger and Dale [2] to denote "manifestations that are tantamount to electrical stimulation of the thoracicolumbar division of the involuntary nervous system, or to stimulation of this same system by adrenalin." Such symptoms include the cardinal clinical symptoms of tachycardia, exophthalmos, goiter and tremor, and the minor symptoms of exophthalmic goiter, such as diarrhea, sweating and palpitation. In these patients there was no alteration in basal metablism, and no evidence that an alteration had even been present. To this clinical syndrome of sympathomimetic symptoms without elevation of the basal metabolism we have applied the term autonomic imbalance. It is solely by the absence of an elevation of basal metabolism that these patients are distinguishable objectively from patients with exophthalmic goiter.

MATERIAL STUDIED

The patients were studied in the wards of the Mount Sinai Hospital.[3] The following points are to be emphasized: (1) The symptoms presented were sufficiently severe to warrant residence in a hospital where beds are at a great premium; (2) the patients in our institution present a racial nervous and emotional instability; (3) the patients come from the poorest sections of the city, and are subject to constant economic strain; (4) the history of fifty consecutive patients is presented irrespective of the end results. An attempt was made to follow each patient. Where contact was lost we regard the case as a failure and so report it.

The abstract of a case history given below is typical of the studies made of each of the patients. Where symptoms could not be measured, the intensity was indicated on the basis of four plus (4 +). Special attention was paid to the sequential history, which detailed the complete life of the patient. This served two purposes: First, to throw light on the natural history of the illness; and, second, to guide in the management of the individual patient.

M. N. (208121), female, aged 26, single, was an art illustrator.

Past Illnesses.—Patient had measles and scarlet fever four times in childhood; pertussis twelve years ago; epidemic influenzal pneumonia two years ago. Her tonsils and adenoids were removed sixteen years ago.

Personal History.—Menses began at the age of 16, occurring every twenty-eight days and were of three days' duration.

2. Barger and Dale: J. Physiol. **41**:19, 1910.

3. The clinical studies were carried out in the wards of the Mount Sinai Hospital on the medical services of Drs. Brill and Libman and in the outpatient department in the classes of Drs. E. Moschcowitz and R. Ottenberg; the laboratory studies, in the department of pharmacology of the College of Physicians and Surgeons, Columbia University. The work has been made possible by a fund established for the purpose by the New York Foundation and by Mr. Felix Warburg.

Sequential History.—The patient was born in Canada. Her life was uneventful until eight years ago when she was told by telephone that her father had been killed. She was greatly shocked and was unable to talk for several days. A few months after this, the goiter was noted but she had no other symptoms. Iodids were administered without effect on the gland. Despite financial reverses, she was well for the next two years. Then she experienced nervousness, exophthalmos, asthenia, tremor and tachycardia, and she lost 30 pounds weight. Her physician regarded her condition as so precarious that he gave her three months to live. She was treated with injections but without benefit. She then came to New York and rested at the home of an aunt where she was carefully nursed. She gained 30 pounds weight and resumed her work in the art school. Because of the unsightliness of her goiter, she sought operative treatment, although she was then symptom free. She entered the hospital, and examination revealed, besides the goiter, only tremor and a pulse rate of 100. A hemithyroidectomy was performed and the specimen was reported to be a parenchymatous and colloid struma. After operation she felt that her condition was unchanged; her goiter was no smaller. A few months later she was desperately ill with pneumonia. She resumed her work in a few months and was well until six months ago when her previous symptoms recurred. She also had a growth on her knee which she was told was tuberculous. She entered the hospital for the removal of this tumor but was prevailed on to

Present Status	3/15/21	5/2	6/16	7/14	8/12	10/8	2/10/22	3/14	10/1
Loss of weight	30 lbs.	Gain	G	G	G	G	—	—	—
Nervousness	4	0	2	1	0	0	0	0	0
Palpitation	2	1	1	1	0	0	1	0	0
Bulging eyes	2	2	2	2	2	1	0	0	0
Goiter	3	2	2	2	2	2	1	0	0
Tremor	3	0	1	0	0	0	0	0	0
Sweating	2	0	0	0	0	0	0	0	0
Flushes	2	0	0	0	0	0	0	0	0
Asthenia	2	0	0	0	0	0	0	0	0
Weight	112	119	—	124	—	128	—	—	—
Pulse	112	100	110	100	—	88	—	88	88
Exophthalmometer	20	—	20	—	21	—	—	17.5	—
Basal metabolism	53	36	16	16	22	5	6	—	—

submit to thyroidectomy. Before this operation examination revealed a pulse rate of 98; exophthalmometer, 20; basal metabolism +10 and +16, and a tremor. The operation was done under local anesthesia; the middle and left lobes were removed, and the report was parenchymatous goiter. She was returned from the operating room in a precarious condition and was desperately ill for five days. She finally went to the country and convalesced nicely. One month ago all her previous symptoms returned with the severity of her first crisis.

Anatomic Status.—The patient was well nourished; her hair was black, streaked with gray; the outer portion of the eyebrows was sparse; systolic murmurs were present at both apex and base with respiratory arrhythmia and dynamic abdominal aorta; a spastic sigmoid was palpable. The digits tapered. Emotionalism and vasomotor instability were marked. Scars were present over the thyroid. A large thyroid remnant persisted, irregular in shape, soft to the touch and with a bruit over it. The nasal septum was deviated. The tonsils were cryptic and half buried. All eye signs were present. Locomotion pulse was present in the vessels of the fundus.

Laboratory Data.—Tests revealed: Hemoglobin, 93 per cent.; red blood cells, 4,200,000; white blood cells, 7,100; lymphocytes, 31 per cent.; platelets, 20,000; bleeding time, 5 minutes (secondary purpura). Urea, 15, incoagulable nitrogen, 40; uric acid, 3; creatinin, 1.55 mg. per hundred cubic centimeters; sugar tolerance test, 113/220/180; occasional albuminuria was noted. Phenolsulphonephthalein, 62 per cent.; reaction to epinephrin was ++++ and to atropin ++++.

TABLE 2.—Preexistent Sympatheticomimetic Symptoms (Autonomic Imbalance) in Patients Now Suffering from Exophthalmic Goiter

	Palpitation	Nervousness	Sweating	Blushing	Cold Extremities	Headache	Psychic Unrest	Loss of Hair	Irregular Menses	"Stomach Trouble"	"Heart Trouble"	Diarrhea	Dyspnea	Polyuria	Polydipsia	Asthenia	Insomnia	Sympatheticomimetic "Score"	Epinephrin Reaction	Atropin Reaction
Males																				
1. Albeck	0	+	+	+	0	+	+	0	—	0	+	0	0	0	+	0	0	7	4	—
2. Preisler	+	+	+	+	0	+	+	0	—	0	0	0	+	0	0	0	0	7	4	3
3. Weinstock	+	+	+	0	+	+	+	+	—	0	0	0	0	+	+	0	0	9	4	0
4. Rosenthal	0	0	0	0	0	0	0	0	—	0	0	0	0	0	0	0	0	0	4	4
5. Cohen	0	0	0	0	0	0	0	0	—	0	0	0	0	0	0	0	0	0	4	3
6. Faber	0	0	0	0	0	0	+	0	—	0	0	0	0	0	0	0	0	1	4	4
7. Wollman	0	0	+	0	0	0	0	0	—	0	0	0	0	0	0	0	0	1	is	2
8. Kantrowitz	0	0	0	0	0	0	0	0	—	0	0	0	0	0	0	0	0	0	—	—
9. Rosenberg	0	0	0	0	0	0	0	0	—	0	0	0	0	0	0	0	0	0	—	—
10. Horowitz	0	+	0	0	0	0	0	0	—	+	0	0	0	0	0	0	0	0	—	—
Females Whose Symptoms Arose Before the 35th Year																				
11. Dunkelman	0	0	+	+	0	0	0	+	+	+	0	+	0	+	+	+	0	9	1	3
12. Berkowitz	0	0	0	0	0	+	+	0	0	0	0	0	0	0	0	0	0	2	4	2
13. Droga	0	0	+	0	0	0	0	0	+	0	0	0	0	0	+	0	0	3	0	—
14. Kurzmack	0	0	+	+	0	+	+	+	+	0	0	0	0	0	0	0	0	6	—	—
15. Naimon	0	0	0	0	0	0	+	0	+	0	0	0	0	0	0	0	0	2	4	4
16. Belford	0	+	+	+	+	+	+	+	+	0	0	0	+	0	0	0	+	10	—	3
17. Juhasz	0	+	+	+	0	+	0	+	0	0	0	0	+	+	0	0	0	7	4	2
18. Meltzer	+	+	+	0	+	+	+	+	+	0	0	0	+	0	0	+	+	10	—	—
19. Tanguay	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	1	4	1
20. Goodglass	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—	—
21. Kraft	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	2
22. Albert	0	0	0	+	+	+	0	+	+	0	0	0	0	0	+	+	0	7	—	3
23. Fox	0	0	0	+	+	+	+	0	0	0	0	0	0	0	+	+	+	8	3	3
24. Cohen	0	0	+	+	0	+	0	0	0	0	0	0	+	0	0	0	0	4	2	4
25. Rodamon	0	0	0	0	0	0	0	0	+	0	0	0	0	0	0	0	0	1	4	4
26. Altman	0	0	0	0	0	0	0	0	+	0	0	0	0	0	0	0	0	1	—	—
27. Fisher	0	0	+	0	0	+	0	0	0	0	0	0	0	0	0	0	0	2	4	2
28. Steinbach	+	0	+	+	+	+	+	+	0	+	0	0	+	0	0	+	0	10	—	—
29. Farber	0	0	0	0	0	0	+	0	0	0	0	0	0	0	0	0	0	1	—	—
30. Goldstein	0	0	+	+	+	0	+	0	0	0	0	0	0	0	0	0	0	4	4	—
31. Handel	0	0	0	+	0	+	+	+	0	0	0	0	0	0	+	0	0	6	4	0
32. Green	0	0	+	0	0	+	0	+	0	0	0	0	0	0	0	0	0	3	4	4
33. Hoffman	0	0	0	0	0	+	0	+	0	+	0	0	0	0	0	0	0	3	4	1
34. Kretman	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	—	0
35. Hamberger	0	0	+	+	+	0	0	0	0	0	0	0	0	0	+	0	0	4	—	0
36. Griffith	0	+	0	+	0	0	+	0	0	0	0	0	0	0	0	0	0	3	4	—
37. Honig	+	0	0	0	0	0	0	+	0	0	0	+	0	0	+	0	+	5	4	4
38. Speigel	0	+	0	+	+	0	+	0	0	0	0	0	0	0	0	0	0	4	—	2
39. Schneider	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—	1
Females Whose Symptoms Arose After the 35th Year																				
40. Belkin	0	0	+	+	+	0	0	+	+	0	0	0	0	0	0	0	0	5	2	4
41. Raskin	0	0	0	0	0	+	0	0	+	0	0	0	0	0	0	0	0	2	4	3
42. Weiner	0	0	+	0	0	0	0	+	+	+	0	0	0	0	+	0	0	7	4	4
43. Kaplowitz	0	+	+	+	0	0	0	+	+	0	0	0	0	+	+	+	0	8	3	1
44. Jandus	0	0	0	0	0	0	0	+	0	0	0	0	0	0	0	0	0	1	1	0
45. Silverstein	+	0	0	0	0	+	0	+	+	0	0	0	0	0	+	0	0	5	3	2
46. Litschstein	0	0	+	+	+	+	0	+	0	+	0	0	0	0	0	0	+	8	3	2
47. Feldman	0	0	0	0	0	+	0	0	0	0	0	0	0	+	+	0	0	3	4	2
48. Glassowitz	0	+	0	0	+	+	0	0	0	0	0	0	0	+	0	0	+	5	—	—
49. Maegelin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0
50. Nacht	0	+	+	0	0	+	0	0	0	+	0	0	0	+	0	0	0	5	2	0
51. Sigismund	0	+	+	+	+	0	+	0	+	+	0	+	0	+	0	0	+	10	0	0
Total	6	14	22	20	12	24	16	19	17	8	1	3	7	9	13	6	8			

* The sympatheticomimetic "score" is obtained by adding the number of symptoms listed. The epinephrin reaction is estimated by the extent of the pressor response (0 = below 12 mm., 1 = 12-15, 2 = 15-20, 3 = 20-25, 4 = over 25); the atropin reaction by the pulse rate variation (0 = below 10 per minute, 1 = 10-15, 2 = 15-20, 3 = 20-25, 4 = over 25). A dash (—) in either column indicates that the test was not done. Note that there is no relationship between "score" and intensity of drug reactions. Compare these symptoms with present symptoms of exophthalmic goiter and with residual symptoms in "arrested" cases.

Course.—The hospital course was complicated by tonsillitis. Roentgen-ray treatment of the tonsils was started. She went to the country for one month and then remained home at full rest for one month. She has been at work ever since. Despite the illness of her mother and trouble with the landlord, she has been free of symptoms for fifteen months.

SUMMARY: Psychic insult; exophthalmic goiter; recovery from first crisis; interval hemithyroidectomy; second crisis; partial thyroidectomy; third crisis; spontaneous recovery; well now for more than a year and doing full work.

ETIOLOGY

Predisposing Factors.—In a small group (10 per cent.) of patients no previous symptoms were noted. In 90 per cent. of the patients, persistent or recurring symptoms existed. When these were tabulated, the syndrome of autonomic imbalance was again reconstructed (Table 2).

Stern [4] has called attention to the presence of a predisposition. He emphasized, as did Charcot,[5] the incidence of functional nervous disorders in this group. Four of our patients had psychoses; two had epileptic convulsions, and two had hysterical aphonia.

TABLE 3.—RÉSUMÉ OF ETIOLOGY IN CASES STUDIED

Condition *	No. Cases	Per Cent.
Psychic insult (alone)	18	35
Psychic insult (associated with other factor)	37	72
Focal infection (tonsils)	14	27
Focal infection (sinuses)	3	6
Focal infection (total)	20	40
Dietary insufficiency	2	4
Sex epoch	4	8
Unknown	9	18

* Associated conditions are not listed. Direct causal relationship must be demonstrable to warrant inclusion in this table.

The predisposing factors bore no relation to the age of the patient, to the duration, or to the type, of thyroid enlargement.

Exciting Causes.[6]—By far the most frequent and important exciting cause was psychic insult. In 72 per cent. of the histories this was in immediate relationship to the onset of the disease. Focal infection played an exciting rôle in 40 per cent., the focus being present almost constantly in either the tonsils or the sinuses. Alterations in sex life and dietary insufficiency were operative in a small number. In many of the patients more than one exciting factor occurred (Table 3).

PATHOLOGY

Two complete necropsies were made. In Case 49, in which death was due to cardiac failure following pneumonia and pericarditis, the

4. Stern: Jahrb. f. Psychol. **29**:179, 1908.
5. Charcot: Clinical Lectures.
6. Under this caption we are not discussing the primary cause of the disease.

thyroid gland was colloid. In Case 8, in which death was due to a psychosis associated with the exophthalmic goiter, the summary of the pathologic findings was: (1) hyperplasia of the thyroid gland; (2) persistent thymus (weight 20 gm.); (3) edema of the lungs; (4) absence of lipoid in the sections of the suprarenal; (5) parenchymatous degeneration of the liver.

SUBJECTIVE SYMPTOMS

Asthenia (88 per cent.), loss of weight (84 per cent.), palpitation (84 per cent.) and nervousness (80 per cent.), were the most frequent symptoms. Of the cardinal symptoms of exophthalmic goiter, goiter was present in 78 per cent., and the subjective presence of exophthalmos was reported in but 60 per cent., and of tremor in 70 per cent. The surprising frequency of dyspnea (62 per cent.), vomiting (30 per cent.), dysphonia (24 per cent.), dysphagia (10 per cent.), headache (28 per cent.), precordial pain (14 per cent.), and pain in the eyes (16 per cent.), is worthy of comment.

Palpitation.—Palpitation bore no constant relation to the heart rate, blood pressure or pulse pressure. It was usually precordial, but at times epigastric. In patients whose symptoms had otherwise been alleviated completely, mental or physical strain sometimes induced sharp attacks of palpitation.

Diarrhea.—The most characteristic type of diarrhea was the passage of frequent, small stools, but the total daily amount of feces was not excessive. The stools themselves were normal. The diarrhea was unaffected by diet and drugs. The patient might continue to gain weight, even when this symptom was distressing. Its occurrence was much more frequent in the group of older women, of whom seven of twelve suffered from this complaint.

Dyspnea.—This symptom was present with surprising frequency. It was not associated with either cardiac or pulmonary disease and was not necessarily present in those with the highest metabolism.

Asthenia.—Asthenia was usually the earliest and most persistent symptom. Of the six patients who did not complain of asthenia, five were males.

Dysphonia.—In none of the patients who had dysphonia was any abnormality present in the larynx. None of the patients had a substernal goiter. Of the four patients who had substernal goiter, none had hoarseness.

Dysphagia.—As with the symptom of dysphonia, no mechanical reasons could be found for this symptom.

Edema of the Feet.—This symptom occurred five times. In one woman it was due to varicose veins; in the others no static, circulatory or renal cause was present.

TABLE 4.—Objective Signs and Laboratory Data in Exophthalmic Goiter *

	Pulse Rate	Systolic Blood Pressure	Pulse Pressure (Actual)	Pulse Pressure (Per Cent.)	Transverse Diameter of Heart	Locomotion Pulse	Palpable Spleen	Lymphadenopathy	Palpable Liver	Tremor (Coarse or Fine)	Mydriasis	Exophthalmometer	Neck Circumference	Thyroid: Consistency (Firm or Soft)	Thyroid: Uniform or Discrete Tumor	Thyroid: Bruit	Thyroid: Substernal	Blood: Lymphocytes (Actual)	Blood: Lymphocytes (Per Cent.)	Blood: Cholesterin	Blood: Sugar (Fasting)	Blood: Sugar (After Glucose)	Basal Metabolism (entrance)
1	104	130	67	51	7.5	0	0	0	0	0	+	—	32	F	U	0	0	2,900	47	148	115	180	37
2	100	162	84	52	N	0	+	+	+	0	+	20	37	—	—	0	0	3,300	28	114	120	130	46
3	100	128	82	65	12	+	0	0	0	C	+	31	38	F	D	0	0	3,100	45	266	107	—	26
4	160	200	100	50	11	0	0	0	0	F	+	N	27	S	U	0	+	2,600	35	—	112	140	46
5	90	132	64	48	N	—	0	0	0	C	0	18	34	F	U	0	0	2,200	42	150	128	340	39
6	92	118	70	59	N	0	0	0	0	C	0	21	36	F	U	+	0	3,000	60	—	90	120	54
7	120	115	37	32	N	+	0	0	0	C	0	22	N	F	U	0	0	2,200	22	90	130	140	35
8	120	164	90	54	N	+	0	0	+	C	+	18	—	F	U	+	0	1,840	28	146	128	380	75
9	80	—	—	—	N	—	0	0	0	0	+	—	..	F	U	0	?	.....	..	—	...	...	..
10	100	138	70	51	N	—	0	0	0	C	+	—	35	F	U	0	+	2,150	43	...	132	—	38
11	120	142	142	100	N	0	0	0	0	C	0	21	31	F	U	+	0	5,400	40	92	210	—	8
12	130	114	—	—	N	—	0	0	0	F	0	23	34	F	UD	0	0	2,600	28	107	100	108	25
13	120	120	50	42	18	+	0	0	0	C	0	19	35	F	U	+	0	3,700	33	138	180	170	40
14	90	124	66	53	N	0	0	0	0	0	+	22	32	F	U	0	0	3,500	45	230	100	...	44
15	112	124	—	—	N	+	0	0	0	0	0	26	—	S	U	+	0	2,200	31	...	113	180	53
16	100	—	—	—	N	+	0	0	0	0	0	23	31	F	U	0	0	1,900	20	...	...	...	18
17	140	144	82	58	12	0	0	0	0	F	0	28	32	S	U	+	0	3,840	60	132	136	...	56
18	120	140	50	36	N	0	0	0	0	F	+	22	34	F	U	0	+	3,850	35	90	90	...	57
19	100	96	96	100	N	0	0	0	0	0	0	21	33	F	U	+	0	.....	..	...	100	85	24
20	126	140	50	36	N	0	0	+	0	F	0	19	29	F	U	0	0	.....	37	...	130	100	35
21	84	110	45	41	N	+	0	0	0	F	+	25	34	F	U	+	0	1,500	38	176	130	138	55
22	110	130	50	38	N	0	0	0	0	C	0	21	35	F	U	+	0	1,400	26	...	...	...	46
23	100	140	90	62	N	0	0	0	0	C	+	21	30	F	U	+	0	1,900	24	120	110	140	20
24	108	144	64	44	N	+	0	0	0	C	+	19	30	F	UD	0	0	1,800	50	...	...	...	17
25	120	132	78	60	N	+	0	0	+	F	+	19	36	S	U	+	0	2,800	35	...	90	170	34
26	90	—	—	—	N	+	0	0	0	0	+	23	33	F	U	+	0	2,900	34	...	116	...	29
27	130	130	70	55	12	0	+	0	+	F	0	17	36	F	U	+	0	2,100	30	...	...	...	48
28	152	120	70	55	18	+	0	0	0	F	0	17	36	F	U	+	0	2,800	36	114	110	...	64
29	130	—	—	—	N	—	0	0	0	F	0	—	31	F	U	0	0	.....	..	...	...	...	100
30	136	138	52	—	N	+	+	0	0	F	+	23	34	F	U	+	0	.....	..	...	...	...	64
31	100	112	50	46	N	0	0	0	0	F	+	20	34	S	U	+	0	3,600	41	...	...	...	58
32	100	138	50	43	16	+	0	0	0	F	+	30	33	S	U	0	0	9,700	61	...	...	...	50
33	100	108	64	59	N	+	0	0	0	0	0	18	N	S	U	0	0	2,000	27	130	110	108	40
34	130	106	56	52	N	+	0	+	0	C	+	17	31	F	U	0	0	2,800	52	...	107	129	36
35	110	118	46	39	N	0	0	0	0	C	0	N	37	S	U	+	0	2,300	30	136	104	113	22
36	120	134	84	62	N	+	0	0	0	F	0	18	N	F	U	0	0	1,600	28	...	100	160	48
37	84	140	95	73	16	+	0	0	0	F	0	27	38	F	U	+	0	4,400	35	...	115	150	35
38	128	150	70	46	N	+	0	0	0	F	+	N	N	F	U	0	0	2,850	22	114	60	240	62
39	100	120	40	33	N	—	0	0	0	C	0	—	—	F	U	0	0	.....	..	...	...	...	37
40	140	150	70	47	N	0	0	0	0	0	0	N	N	F	U	0	0	2,000	30	...	...	...	30
41	84	110	45	41	N	+	0	0	0	0	0	15	30	S	U	0	0	4,100	50	...	135	250	48
42	120	140	85	60	14	+	0	0	0	F	+	19	33	F	U	+	+	3,200	50	132	115	...	68
43	110	148	68	47	N	0	+	0	+	C	+	18	34	F	U	+	0	1,100	24	...	95	...	47
44	138	97	47	48	N	+	0	0	0	F	+	N	N	F	U	0	0	2,800	35	130	...	...	63
45	90	140	50	36	N	0	0	0	0	0	0	17	28	F	UD	0	0	3,400	50	...	...	...	28
46	120	170	80	47	N	+	+	0	0	C	+	21	27	F	U	0	0	2,600	28	130	85	260	50
47	112	100	65	65	N	+	+	0	0	0	+	18	27	F	D	+	+	2,250	45	...	140	150	42
48	? †	170	70	41	18	0	0	0	+	F	0	N	37	F	D	0	0	2,700	17	...	...	...	48
49	? †	120	70	58	N	0	0	0	+	0	0	14	31	F	UD	0	0	2,100	28	130	78	113	50
50	130	200	200	100	14	0	0	0	0	0	0	17	N	F	U	0	0	3,700	35	...	136	240	57
51	100	160	100	62	14	0	0	0	0	C	0	N	35	F	D	0	+	3,680	40	132	60	240	57

* Pulse pressures were all above 40 mm. Hg and 30 per cent. In older women, fine tremor was unusual, exophthalmos usually was below 20 and neck circumference rarely exceeded 30 cm. except when there was a large discrete tumor. In younger women, fine tremor was more frequent, exophthalmos usually exceeded 20 and neck circumference was greater than 30 cm., due to diffuse and uniform thyroid enlargement. Bruit was not necessarily present in the severest cases. Lymphocytosis invariably was present but did not parallel the severity of the disease. Cholesterin usually diminished in amount but not in inverse relation to the basal metabolism elevation. Sugar tolerance test was frequently normal. Basal metabolism and pulse rate were not necessarily elevated correspondingly

Pain in the Eyes.—In two of the eight women who complained of this symptom, the exophthalmos was very slight.

OBJECTIVE SYMPTOMS (TABLE 4)

Skin and Appendages.—Fifty per cent. of the patients presented the scanty eye-brows so characteristic of myxedema. Five patients had a generalized diffuse brown pigmentation. In one of these patients the disease was acute.

Laryngeal and Rhinologic Findings.—(Drs. Yankauer and Kaempfer). Without exception, foci of infection were present in the nose or throat in all cases. Purulent secretion was expressed from the tonsils of all patients; four had hypertrophied lingual tonsils, and five had sinus infection. Activity in these foci, or reinfection, at times caused serious and protracted remissions of the exophthalmic goiter. Surgical drainage of a sinus or tonsillectomy often alleviated the symptoms.

Tachycardia.—The great difficulty in obtaining a basal pulse rate detracts from the importance of this constant symptom. The lability of the pulse rate is so great that it is practically impossible to obtain a satisfactory norm. Pulse rates taken during sleep often, but not invariably, showed a marked decrease. A comparatively slow pulse was observed with relatively high metabolism (Cases 6, 21, 37 and 45). A marked decrease in metabolism occurred without slowing of the pulse rate (Cases 25, 27, 28 and 31). Digitalis did not alter the tachycardia.

The Heart.—Twelve patients showed definite enlargement. In none was there an accompanying valvular defect. In three of these cases, the electrocardiogram showed left ventricular preponderance. In two others of this group there was auricular fibrillation.

Cardiac Sounds.—In many of the patients the snap of the first apical sound and the accompanying thrill simulated closely the signs in mitral stenosis. In only one (Case 27) could we feel sure that a true stenosis existed. Systolic murmurs at the apex and base were common and of no significance.

Electrocardiogram.—Auricular fibrillation was seen in four patients. In one (Case 45), the attack was transitory during a bronchopneumonia. In Cases 48, 49 and 51 the fibrillation was persistent. In Case 48 quinidin, and in Case 51 digitalis, was without effect. All of these women were in the older group and none had substernal thyroids. The absence of left ventricular preponderance in the majority of patients with cardiac enlargement was thought to indicate a concentric hypertrophy.

Blood Pressure.—Cases 2 and 50 had a definite hypertension in the absence of cardiorenal disease. Lability of the blood pressure was striking, the systolic pressure varying between 140 and 220 mm. of mercury.

Pulse Pressure.—In every instance the pulse pressure was distinctly increased, both on an absolute and a percentile basis. Diastolic pressure was low in all, and in three patients (Cases 11, 19 and 30) the sounds could be heard at zero. This was a temporary phenomenon. In none of these patients was aortic disease present.

Spleen and Superficial Lymph Nodes.—The associated enlargement of these structures was surprisingly frequent. In none of the patients was there any obvious explanation for the adenopathy. In acute febrile cases the enlargements were frequent and often painful. In one patient (Case 30) these organs enlarged strikingly as the result of an epinephrin reaction.

Tremor.—The rapid fine tremor of exophthalmic goiter was no more frequent than a coarse, slow, irregular tremor. The latter was encountered particularly in the group of older women.

Exophthalmos.—The relationship between the presence of exophthalmos and the age of the women at the onset of the disease as noted by Trousseau [7] was confirmed. In the younger group of patients, who developed their illness before the age of 35, the bulging was striking and was rarely below 20 mm. In the older group, exophthalmos was frequently absent, and if present was rarely marked; in only one of the twelve women in this group did the measurement exceed 20 mm.

Plummer [8] regards exophthalmos as a most important differential point in the diagnosis of toxic hyperplastic and toxic nonhyperplastic goiters. It is his belief that an alteration in the construction of the thyroxin nucleus determines the production of the exophthalmos. The striking rôle of the age of the patient, as demonstrated above, indicates that it is a change occurring in the end organs rather than an alteration in the thyroid structure or secretion that determines the presence of this symptom. The degree of the exophthalmos does not parallel the severity or progress of the disease.

Exophthalmos is not pathognomonic and can be observed in otherwise normal patients and in those with autonomic imbalance.[1]

Ocular Manifestations.—(Drs. Schlivek, Wolff, Barnett and Tenner). The ocular manifestations seem to have been greatly overemphasized.[9] Any or all of the classical signs may be present in normal people or in those with autonomic imbalance. Furthermore, these signs

7. Trousseau: Clinical Lectures, published by the Sydenham Society.
8. Plummer: Tr. A. Am. Phys., 1916, p. 138.
9. Sattler: Die Basedowische Krankheit, Engelmann, 1909.

are transitory. Aside from the exophthalmometer readings, the most valuable sign in our experience has been the locomotion pulse of the vessels in the fundus oculi.

Goiter.—Fourteen per cent. of the patients had a thyroid gland that was visibly and palpably normal. A normal or very slightly enlarged gland was the rule in the group of the older women. The consistency of the glands varied. Six patients presented enlargements that were due to discrete nodules within the substance of the gland, presumably either cysts or adenomas. Two of these six patients (Cases 12 and 24), both younger women, had exophthalmos. The remaining four (Cases 45, 48, 49 and 51) of the older women had no exophthalmos. Eight patients had substernal goiters; none of these had pressure manifestations. Thrills, bruits and murmurs were present over the gland in twenty patients; the presence or absence of these bore no relation to the severity of the disease. "Goiterophobia" was the cause of unusual mental distress in many of the patients.

Anthropologic Make-Up.—We did not constantly encounter the thyroidal "type" of the endocrinologists. Many of the patients were of the thyroid habitus, as many had the characteristics of the other so-called "endocrine types." That this was due to associated involvement of other endocrine glands seems a rather poorly constituted biologic argument.

The Liver.—In both patients who came to necropsy the liver was extremely small, though in neither was there cirrhosis.[10]

Fever.—In the acute cases and in acute exacerbations fever was present. When it accompanied psychoses it was of serious prognostic omen.

Loss of Weight.—The weight usually furnished an excellent index of the progress of the disease. Maintenance of weight or tendency to gain was a favorable prognostic index. The gain of weight was often quite extraordinary, and might proceed in spite of a constantly and greatly elevated metabolism (Cases 29 and 51).

The Endocrine System.—The problem of polyglandular involvement is so difficult of approach that we shall limit ourselves to a discussion of clinical findings. The observations on the thyroid have been mentioned previously. At the necropsy in Case 8 a persistent thymus and a diminished suprarenal cortex were found. This patient also had atrophic testes, but the atrophy was no more marked here than in the other parenchymatous organs. Menstrual irregularities were definitely associated with the disease in eight patients. The type of the disturbance was not constant and the pelvic contents were normal.

10. Marine, David: Bull. Johns Hopkins Hosp. **28**:359, 1907.

Hematologic Findings.—The hemoglobin and red cells were normal. In all but three patients there was a relative and absolute lymphocytosis. There was no definite relationship between the severity of the disease and the degree of lymphocytosis.

Metabolism.—The blood constituents showed no constant alteration. The nitrogenous products were normal except in Case 8 at the time of the febrile psychosis, when, in the face of normal renal function, the values rose considerably. The increase consequently was a catabolic phenomenon. Except for the increase in this same patient, the uric acid and creatinin values were normal. With one exception all of the patients had a blood cholesterol well below the upper limit of normal. The diminution in the cholesterol content was no accurate index of the severity of the disease. Sugar tolerance[11] tests were made on twenty-seven patients; in nine the return to normal was obtained within two hours. This test, consequently, was not sufficiently constant to be a reliable diagnostic sign.

The oxygen consumption was determined in the estimations of basal metabolism. To establish the diagnosis of exophthalmic goiter in clearly defined cases, such as these, the basal metabolism is of little value. In another place[1] we have discussed its crucial value, however, in the exclusion from the group of exophthalmic goiter of patients with autonomic imbalance. We have arbitrarily chosen to accept the basal metabolism as the best available objective diagnostic sign.[12] For the present we do not accept as exophthalmic goiter a case in which there is not, or has not been, a constant and distinct elevation of the basal metabolism. For the estimation of the progress of the disease it is unquestionably the best objective index.[13] There are, however, striking exceptions to this, and patients may have severe manifestations of the disease and a slight elevation of metabolism (Case 3), or they may be progressing favorably and the metabolic elevation (Case 29) persist unchanged.

We have included one patient (Case 11), whose metabolism was never above + 8. This girl was 13 years of age, her height was 66 inches and her weight 135 pounds. Her oxygen consumption was distinctly elevated, but the normal figures for her age brought her basal metabolism within normal limits. In view of the clinical findings in this patient, we were compelled to ignore the metabolic test.

Drug Reactions.—In Table 5 will be found the results of the atropin and epinephrin tests. Two patients (Cases 12 and 13) did not respond to epinephrin. There was no constant relationship between the pressor

11. Janney and Henderson: Arch. Int. Med. **26**:297 (Sept.) 1920.
12. DuBois: Arch. Int. Med. **17**:915 (June) 1916. Means and Aub: Arch. Int. Med. **24**:645 (Nov.) 1919.
13. Means and Aub: J. A. M. A. **69**:33, 1917.

and accelerator reactions, nor between the circulatory response and the subjective or objective symptoms. The severity of the epinephrin reaction may be so great as to be alarming. The drug should never be administered at the height of the disease, and a preliminary injection, not exceeding 0.2 or 0.3 c.c. should be made.

The atropin response was absent in only 24 per cent. of the patients tested. It bore no relation to the epinephrin response, to the symptoms

TABLE 5.—Responses of Patients with Exophthalmic Goiter to Epinephrin and Atropin Injections

Name	Before Epinephrin		After Epinephrin		Minims Epinephrin Used	Pulse	
	Pulse	Blood Pressure	Pulse	Blood Pressure		Before Atropin	After Atropin
Albeck	110	120	116*	142*	5	...	...
Albert	...	...	...	...	...	102	132*
Belford	...	...	...	...	...	78	120*
Belkin	96	120	104*	138*	5	76	128*
Berkowitz	100	114	122	118	5	100	130*
E. Cohen	108	126	114*	152*	5	100	140*
Dunkelman	120	136	148*	156*	7	114	132*
Droga	128	120	136	126	5	...	...
Faber	106	110	130*	150*	3	104	120*
Feldman	110	120	204*(?)	184*	7	112	126*
Fox	72	110	108*	138*	7	80	106*
Fisher	...	126	...	178*	3	108	128*
Goldstein	130	138	156*	180*	3	...	...
Green	...	96	...	160*	7	108	132*
Griffith	106	114	118*	198*	5	106	110
Hamburger	...	...	...	...	...	112	120
Handel	100	104	120*	160*	5	108	104
Hoffman	93	94	116*	138*	5	104	108
Honig	80	104	96*	142*	5	80	106*
Jandus	124	130	128*	154*	5	124	134*
Kaplowitz	116	122	132*	160*	7	120	132*
Kraft	104	106	124*	160*	5	104	132*
Litschstein	110	160	130*	188*	3	120	148*
Maegelin	...	...	...	...	...	108	184*
Nacht	120	170	124*	192*	7	130	120
Naimon	96	130	120*	160*	5	92	118*
Preisler	126	124	138*	170*	5	112	138*
Raskin	82	104	112*	188*	5	84	106*
Rodamon	70	124	70*	170*	4	120	156*
Rosenthal	120	130	132*	150*	2	116	164*
Sigismund	92	134	100*	146*	7	102	100
Silverstein	...	...	...	...	...	96	122*
Spiegel	...	...	...	...	...	130	142*
Tangual	100	108	100*	126*	7	112	140*
Weiner	100	130	136*	154*	7	112	134*
Weistein	90	100	100*	112*	5	90	74
Wollman	106	114	130*	140*	6	112	116

* Positive response.

Recapitulation: Of 34 patients tested with atropin, 26 reacted, or 76 per cent.; of 31 patients tested with epinephrin, 29 reacted, or 93 per cent.

or to the severity of the disease. The initial vagus center action was usually present and bore no relation to the epinephrin response. It should again be emphasized that both these reactions may occur in normal persons, and particularly in patients with autonomic imbalance.

The interpretation of the sensitiveness to epinephrin has recently come in for a great deal of comment.[14] We have shown that sensitization to epinephrin may occur in the complete absence of the thyroid

14. Lieb, C. C., and Hyman, H. T.: Am. J. Physiol. **63**:60, 88 (Dec.) 1922.

gland, and that the alleged synergism between thyroxin and epinephrin and the alleged action of thyroxin on the involuntary nervous system are based on an erroneous interpretation of laboratory data.

The subjective manifestations resulting from the epinephrin injection closely mimicked the original complaints of the patients.

Psyche.—These patients were characteristically sensitive, restless and emotionally unstable. Four patients had true psychoses; in two of these, death occurred. When the psychosis is associated with fever, the prognosis is particularly poor.

TYPES OF DISEASE

Two factors were revealed as determinants in the clinical variety of the manifestations of the disease. Of these, the first was the existence of the predisposition (autonomic imbalance). Its importance lay in the fact that the prognosis in patients with predisposition must include the statement that complete symptomatic recovery could not be anticipated. The best that therapy can afford is a restitution to autonomic imbalance with the persistence of these residual symptoms. The second and more important factor in determining the type was the age of the patient at the onset of the disease. It was noted (Table 4) that in the older group of women exophthalmos was comparatively infrequent and rarely measured more than 20 mm., the goiter was rarely large, except when the enlargement was due to a discrete tumor within the gland. The drug reactions in this older group were rarely intense (Tables 2 and 5), a fine tremor was seldom encountered but auricular fibrillation and diarrhea were much more frequent than in the younger group. Of the classical symptoms of exophthalmic goiter in women whose disease began after their thirty-fifth year, tachycardia alone was constant—the exophthalmos, diffuse hypertrophy of the thyroid and the tremor being more frequently absent. The basal metabolism estimation in this group, fortunately, was usually high and out of proportion to the clinical manifestations. We [1] have called attention to the frequent occurrence of the cardinal symptoms of exophthalmic goiter in patients who have no elevation of the basal metabolism. To this syndrome we have applied the name autonomic imbalance, and it is differentiated objectively solely by the basal metabolism estimation.

Other attempts to subgroup our patients were essayed and abandoned. Division into sympathotonic and vagotonic groups [15] based on drug reactions was not clearly defined. A subgrouping on an anatomic basis, as suggested by Plummer,[7] did not hold. Plummer subgroups his patient into toxic nonhyperplastic and toxic hyperplastic, using as criteria the duration of the thyroid tumor before the onset of symp-

15. Eppinger and Hess: Vagotonia, Nerv. & Ment. Dis., 1917, Monograph 20.

toms, its histologic appearance and the presence of exophthalmos. While no histologic material is available in our cases, the subdivision according to the presence or absence of exophthalmos seemed usually related to the age of the patient and independent of the nature of the thyroid enlargement or its duration.

MANAGEMENT

The patients were placed under as nearly ideal hygienic and psychic conditions as is possible in the wards of a large general hospital. A high caloric diet was ordered (about 3,000 calories). Both nurse and patient were instructed that gain in weight was essential to recovery. Wet packs at 75 F. were given for the symptomatic relief of restlessness, insomnia and sweating. In many patients, colon irrigations were given without any definite rationale and without any definite amelioration of symptoms. Phenobarbital (luminal), 1½ grains, was used as a hypnotic. Aside from iodin (syrup of ferrous iodid), given to reduce the neck circumference,[16] no other drug was generally employed.

By means of the sequential history, the confidence of the patient was won and a definite exciting cause, usually psychic or infectious, revealed. When a direct exciting relationship to focal infection was demonstrable, surgery was restored to, with results that were occasionally excellent.

The patients were told that operation would not be necessary and that an attempt would be made to restore them to economic usefulness, though a few of their symptoms might persist. On discharge, they were warned that they were to regard themselves not as cured, but in an arrested condition and that it was necessary for them to take particular care of themselves and for their families to take particular care of them, without coddling. The demonstration to the active patients of those whose disease was arrested was a therapeutic boon.

Only one specific therapeutic endeavor is recorded. In two patients (Cases 6 and 14) an acute exacerbation of symptoms, accompanied by fever (febrile crisis), occurred. Intravenous injection of thyroxin was followed in forty-eight and sixty hours, respectively, by lysis and a striking improvement in the entire clinical picture. The patients had previously seemed to be on the verge of death.

COURSE AND PROGNOSIS (TABLE 1)

There was a tendency to recovery in these patients that was gratifying, even astounding, and to which, at present, we are inclined to attribute many, if not most, of the so-called cures. As a rule, the patients were kept in bed for from six to ten weeks. Of the sub-

16. Marine, David, and Kimball, O. P.: Prevention of Simple Goiter in Man, Arch. Int. Med. **25**:661 (June) 1920.

jective symptoms, asthenia and palpitation persisted most constantly. The other symptoms were usually alleviated. Of the objective manifestations, the goiter, exophthalmos and basal metabolism elevation persisted, but were distinctly lessened.

The patients were then sent to the country for a month. The majority of the women went to the Loeb Home, where the intelligent cooperation of Mrs. Israel, the superintendent, did much to secure for them the mental and physical rest they so greatly needed. Most marked, during this period was the large gain in weight. Further diminution in the symptoms occurred, and at the end of that time economic restitution was possible, though symptomatic cure seldom occurred.

Exacerbations occurred several times, always subsequent to a tremendous psychic trauma or an acute infection, usually tonsillitis or sinusitis. One patient (Case 6) had a true recurrence following overwork and acute tonsillitis. Practically all of the patients have been observed for more than a year and are still under our care.

Several additional clinical points are to be observed in rendering a prognosis: (1) After the fiftieth year, the prognosis is poor. (2) Complete recovery should never be expected, especially in those patients who have had a previous autonomic imbalance. (3) Those patients with many symptoms and a slight metabolic elevation often run a protracted course. (4) A catabolic accumulation of products in the blood is of evil omen. (5) Similarly, with a febrile crisis or psychosis, the outlook is precarious. (6) Favorable indications are: gain in weight; acute onset in a previously healthy person; social and economic freedom, and the presence of sufficient ignorance on the part of the patient to insure strict obedience, or sufficient intelligence to insure helpful cooperation.

DISCUSSION OF RESULTS

Fatal Cases.—Five patients died. Of these, one died as the result of a hemorrhage from a gastric carcinoma and another died from cardiac failure following pyelitis, pneumonia and pericarditis. Two deaths were directly due to the exophthalmic goiter. Of these, one patient (Case 38) was observed by us only two days. She was admitted with a febrile psychosis and it was necessary to transfer her to the psychopathic ward at Bellevue Hospital, where she died later. The other patient (Case 9) died in our wards with a febrile psychosis and an intense accumulation of catabolic products in the blood stream. The fifth death occurred in a young girl (Case 14) during her convalescence. This was a status death. She had been admitted to the hospital with a febrile psychosis. After a febrile period of three weeks, thyroxin, 3 mg., intravenously, was followed in forty-eight hours by lysis and complete recovery. She was sent to the convalescent home,

and there, after a few weeks of steady improvement, experienced headaches. While suffering one of these, she had a convulsion and died. Necropsy revealed the findings typical of status and nothing else. This patient had had a subtotal thyroidectomy in Russia seven years previously.

Failures.—Two cases are reported as complete failures. One patient (Case 19) has been lost from sight, but we feel that she would have kept in communication with us had her condition been satisfactory. (This patient since reports herself as economically restored.) The second failure was in a woman, aged 53, with auricular fibrillation and persistent diarrhea (Case 50). Surgical intervention was suggested, but the surgeons did not regard her as a sufficiently safe risk to attempt operative interference.

Remissions.—One man (Case 6) had a real remission following overwork and an acute tonsillitis. He had been well for one year previously.

Economic and Social Incapacity.—(Table 1). Three patients are still economically incapacitated. Of these, one (Case 51) is still suffering sufficiently from her disease to make her useless socially. She has improved, however, and is still improving steadily. The other two patients who are incapacitated (Cases 46 and 48) have both improved greatly as far as the symptoms referable to the exophthalmic goiter are concerned, but the former has suffered an acute hydrops of the gallbladder, and the latter is decompensated as the result of auricular fibrillation. It will be observed that one of the two failures and the three women who are still incapacitated are the oldest members of the group.

Return to Economic Status.—(Table 1). Forty-one, or 82 per cent., of these patients have been socially or economically restored. Of these, twenty-seven, or 54 per cent., were restored within four months, and four, or thirty-one patients all told, within six months of their hospital entry. The protracted recoveries were almost invariably complicated by some other factor, such as sinusitis, pregnancy or continued psychic trauma. Four of these female patients have successfully completed pregnancies.

These forty-one patients, together with the three who, though still incapacitated, are yet making strides toward recovery, make forty-four patients in whom the spontaneous course of the disease has been toward recovery on an economic basis. In the large majority of cases economic restitution may be anticipated within six months, and in a fair majority within four months. In but one of these patients, the majority of whom have been followed now for a year or more, has a true remission occurred.

It should again be emphasized that we refer here to economic recovery. Symptomatic recovery does not occur completely in these patients. Palpitation and tachycardia on exertion, a certain degree of thyroid enlargement and exophthalmos, do not completely and permanently disappear in any case. These patients are not cured, but their disease is in a stage of arrest. This report, furthermore, is not final. These patients are still under observation and will be maintained so indefinitely. This report is inclusive up to June, 1922.

Nevertheless, the restoration of forty-four of fifty patients to economic recovery in so short a time is sufficient to emphasize pointedly the tendency of this disease to spontaneous arrest in the vast majority of instances.

BASAL METABOLISM AS INDEX OF PROGRESS

In addition to the use of the social and economic restitution as an index of the course of the illness in these patients, we have followed the basal metabolism. This is beyond doubt the most useful objective criterion with which to estimate the course and end result in exophthalmic goiter. Of the fifty-one patients recorded we have satisfactory data of forty-five. Six patients did not have a sufficient number of readings. Among these were four fatal cases, and in the case of the two patients who remained alive (Cases 5 and 10) readings could not be made because of the refusal of the patients to submit to further tests. Both of these patients, however, are progressing favorably and have been at work for the past few months. Of the forty-five on whom sufficient data are available, thirty-two, or 71 per cent., (Table 1) at present have a basal metabolism of less than plus 18 per cent. Of these, twenty-one had fallen to below plus 18 per cent. within four months. Five other patients have fallen to below plus 25 per cent. In other words, thirty-seven of the forty-five patients, or 82 per cent., have fallen to below plus 25 per cent., and in the majority of these, the fall has occurred within four months.

Nine patients still have a basal metabolism exceeding 25 per cent. In only one woman has the metabolism risen under observation. This patient (Case 51) is the oldest member of the group, and though her metabolism remains elevated, she is slowly losing her symptoms.

In the one patient in whom a true recurrence was observed (Case 6), the basal metabolism rose. In one patient (Case 13), the metabolism rose with an exacerbation. Temporary elevations were observed also in seven other patients. These were all definitely associated with the presence of conditions other than active exophthalmic goiter, such as acute gastro-enteritis, sinus infection, pregnancy, psychic insult. All of these causes will be recognized as exciting factors in exophthalmic goiter and emphasize the necessity of maintaining the closest scrutiny over these patients far into their convalescence.

The correspondence of the restitution to economic usefulness, and the fall in the basal metabolism is very striking. There are, however, a few notable exceptions in which economic restitution occurred without a fall in the basal metabolism. Thus one patient (Case 17) was able to do her housework and be symptom free with a basal metabolism of plus 52 per cent. on repeated examinations. Furthermore, this woman gained weight even with this elevated metabolic cadence.

The fact that a striking and persistent fall in basal metabolism occurs in the vast majority of these patients; that this fall persists in the majority of them, even under the most adverse social and economic conditions, must serve to indicate strongly that there is in this disease a marked tendency toward restitution to normal, in patients who receive no specific therapy ("spontaneous course").

The use of the figures obtained in this group of patients when plotted should serve to act as a valuable index in the evaluation of specific therapeutic procedures.[17]

CONCLUSIONS

1. A careful study of the course of fifty patients suffering from exophthalmic goiter is presented.

2. An attempt was made to ascertain the natural or spontaneous course of the disease. While this could not be accomplished, at least no "specific" measures were attempted.

3. Special care was taken to follow these patients after their discharge from the hospital, and attempts will be made to continue to maintain these patients under observation.

4. The disease seems often to develop on the basis of a diathesis (autonomic imbalance).

5. Focal infection, sex epochs and psychic insult are frequent exciting causes.

6. Pathologic studies usually reveal a universal cellular involvement. Thyroid hyperplasia is neither specific nor constant in the findings, and only by unmerited inferences can a fundamental etiologic rôle be ascribed to the alleged hyperthyroidism that supposedly accompanies hyperplasia.

7. Variation in the clinical picture was not due to alteration in the thyroid architecture. Adenoma may be seen with any type of disease. Only by unmerited inferences can a fundamental etiologic rôle be ascribed to adenomas or to their supposed increased or toxic secretion.

8. The symptoms of exophthalmic goiter are almost all sympathomimetic.

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17. Kessel, Leo; Lieb, C. C., and Hyman, H. T.: A Study of Exophthalmic Goiter and the Involuntary Nervous System, IX. An Estimation of the Pathogenesis and the Evaluation of Therapeutic Procedures in Exophthalmic Goiter, J. A. M. A. **79**:1213 (Oct. 7) 1922.

9. The fully developed syndrome is marked by an elevated metabolic cadence as best measured by the basal metabolism. By this alone can this disease be differentiated from autonomic imbalance. In the stage of arrest, differentiation can be made only by the history of the crisis.

10. The clinical picture varies as the age of the patient at the time of onset of the disease. In other words, the variation, especially in regard to the presence and extent of the exophthalmos, is dependent on the end tissues of the patient, rather than on the specific elaboration of any toxic product.

11. In women who develop the disease after the thirty-fifth year, exophthalmos is mild, if present at all; diffuse enlargement of the thyroid is more often absent than present; hoarseness and fine tremor are rare, and diffuse pigmentation, diarrhea and auricular fibrillation are comparatively frequent.

12. Complete restitution to the normal rarely, if ever, occurs. Exophthalmos, thyroid enlargement, lability of the pulse rate and the sympathomimetic symptoms do not entirely and permanently disappear.

13. A response to atropin and epinephrin, injected subcutaneously, is usually, but not invariably, obtained. Epinephrin sensitiveness has nothing whatever to do with thyroid function.

14. The spontaneous course of exophthalmic goiter is toward arrest in the vast majority of cases. In patients who develop the disease late in life (after 45 or 50) the prognosis is poor. If these cases be excepted, the prognosis is excellent under a regimen of "skillful neglect."

15. To establish the efficacy of any specific therapeutic measure, one should demand that definite proof be offered that the results obtained are better than these reported here of the "spontaneous" course of the disease.

16. Until a specific diagnostic test is discovered, no reported case of exophthalmic goiter should be accepted as a genuine case unless the basal metabolism is distinctly and repeatedly elevated.

GENERAL CONCLUSIONS (ARTICLES I-IX)[18]

1. Thyroid hyperplasia and thyroid adenoma may exist for years without at any time causing sympathomimetic symptoms or alteration in metabolism.

2. Disturbances of the involuntary nervous system clinically occur frequently (autonomic imbalance).

3. Such disturbances are usually not attended by metabolic elevation.

4. While these clinical manifestations of disturbances of the involuntary nervous system (autonomic imbalance) are often associated with

18. I-II, Am. J. M. Sc. **165,** March, 1923; III, Arch. Int. Med. **31,** March, 1923; IV-VII, Am. J. Physiol. **63**:60, 68, 83, 88 (Dec.) 1922; VIII, J. A. M. A. **79**:1099 (Sept. 30) 1922; IX, J. A. M. A. **79**:1213 (Oct. 7) 1922.

thyroid hyperplasia, there is no reason to believe that the thyroid enlargement is causative and many reasons for thinking that it is secondary and symptomatic.

5. In exophthalmic goiter the dominant derangement is in the realm of the involuntary nervous system. This may not be primary, but the primary cause, whatever it be, must at least operate through the mediation of the involuntary nervous system.

6. The primary cause of exophthalmic goiter must be sympathomimetic.

7. There is a close relationship between exophthalmic goiter and autonomic imbalance. The latter usually presages the former, and is probably a stage in its development.

8. Evidence is presented to show that thyroxin is not sympathomimetic either directly or indirectly through synergism with epinephrin even if it be granted that epinephrin controls the involuntary nervous system either in the tonic state or in emergency.[19]

There is a marked tendency in patients with exophthalmic goiter to recover spontaneously. This factor must be carefully considered in evaluating "specific" therapeutic procedures.

Miss Grace Mayer has acted as volunteer secretary since the beginning of this work. She has kept the records, arranged the files, kept in communication with the patients and assumed all the burdensome details pertaining to the publication. It is in no perfunctory spirit that we acknowledge our appreciation to her for her unflagging effort, her conscientiousness and her intelligent cooperation.

We wish to express our appreciation to Miss N. C. Bragaw, medical supervisor, for her unusual assistance in caring for these patients.

19. Lieb, C. C., and Hyman, H. T.: Am. J. Physiol. **63**:68, 83 (Dec.) 1922.